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REORGANIZATION OF MOTOR FUNCTION IN THE CEREBRAL CORTEX OF MONKEYS DEPRIVED OF MOTOR AND PREMOTOR AREAS IN INFANCY*

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INTRODUCTION

ABLATION of the motor and premotor regions (areas 4 and 6 of Brodmann; Fig. 1) from the cerebral cortex of the *adult* monkey profoundly affects motor

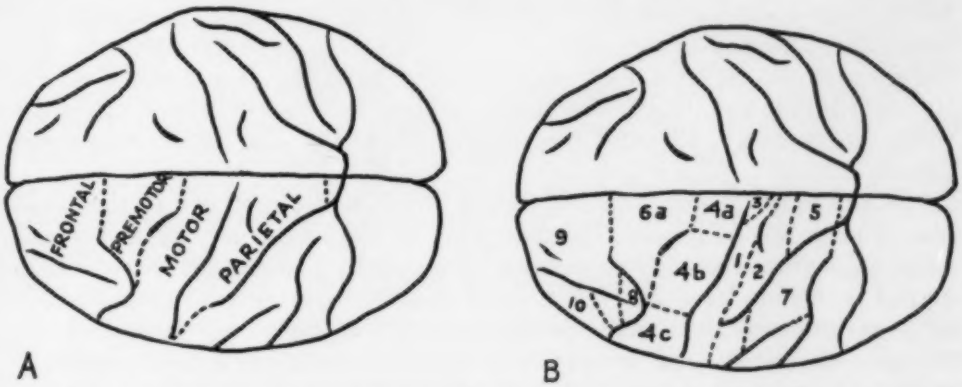

FIG. 1. A. Diagram of cerebral cortex of *Macaca mulatta* showing approximate boundaries of the areas extirpated: the "motor" regions, *i.e.*, motor and premotor areas; and the regions not primarily concerned with motor function, *i.e.*, the frontal and parietal areas.
B. Map of the cerebral cortex of *Macaca mulatta*. (Modification of Brodmann's numerical designation.)

performance of the contralateral, and to some extent also of the ipsilateral, extremities.[4] Immediately after such a bilateral lesion motor capacity is little greater than that of the "thalamic" monkey of Magnus[9,2]; *i.e.*, tonic neck and labyrinthine reflexes can be evoked, but the animal is unable to right itself and cannot readily swallow food, even when placed in its mouth. The longest period during which such a preparation has been observed in this Laboratory is 48 days; during this interval recovery of motor power was minimal, the thalamic reflex status persisted and the animal was unable to right itself or to carry food to its mouth at the end of the seventh week (Bieber and Fulton,[2] Expt. 3). In contrast to this, after removal of areas 4 and 6 from an *infant* monkey, a type of motor performance develops which has conspicuous intricacy and speed as compared with that of older animals following similar lesions; indeed, such infants can walk, climb, and feed themselves and are even able to perform movements of prehension.

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In a previous series of experiments[6] it was shown that in the *adult* monkey after any cortical lesion a number of factors affect the rate and extent of motor recovery. Bilateral ablation of areas 4 and 6 deprives an adult of virtually all "volitional" movement; yet, if one part of either area remains, some purposeful movements are regained. So, although discrete parts of the motor area are known to integrate isolated movements of face, arm or foot, each part of the motor area appears, in addition, to be capable of mediating reactions in other extremities.

There is evidence in addition that cortical fields other than areas 4 and 6 play a part in elaborating motor activity; thus primary removal of the frontal association areas, or of the parietal lobe, has little effect on motor performance; *yet if one or more of these regions is removed in conjunction with areas 4 and 6,* the resultant disability is greater and lasts longer than in animals in which areas 4 and 6 alone are destroyed.[6] The slight recovery appearing after bilateral ablation of areas 4 and 6 may owe its existence to these regions. The duration of the interval between successive ablations also directly affects ultimate motor capability. When the interval is long enough to allow the maximum recovery, a second operation is followed by less deficit; when performed earlier, paresis is greater.[6]

In the *infant* monkey all the factors which affect recovery in the adult also obtain; but in infants, the extent of recovery after any given cortical ablation is always much greater than in the adult. The present paper is concerned with a study of this restitution of function and with the identification of the regions, either cortical or subcortical, responsible for mediating the highly skilled acts which develop in infant monkeys in the complete absence of the classical motor cortex.

TERMINOLOGY AND METHOD

For purposes of exposition the cerebral cortex may be divided into two parts: (i) the areas of accepted motor function and (ii) the remainder of the neopallium in which motor activities are ordinarily overshadowed by other functions. (Fig. 1.) The "motor" regions consist of the motor and premotor areas (*i.e.*, areas 4 abc and 6 ab upper part of the Vogt's modification of Brodmann's map, Fig. 1B), which, in the adult monkey, are essential for purposeful movements. The regions of less conspicuous motor function are: (i) the frontal association areas (areas 8-12 of Brodmann) *i.e.*, all cortical tissue in the frontal lobe rostral to the "motor" areas; (ii) the postcentral gyrus (areas 3-1-2) and part of the posterior parietal lobule (area 5 of Brodmann). It is recognized that area 8, the motor region for conjugate eye deviation, is also a motor area, but for various reasons it has been placed in the second category, since its effect on the motor performance of the extremities with which this paper is chiefly concerned is insignificant.

Observations have been made on 15 infant monkeys, 12 rhesus (*Macaca mulatta*) and 3 baboons (*Papio papio*) born in Laboratory. The procedure consisted in removing portions of cortical tissue from one hemisphere under ether anesthesia, during the fourth week of life. The infants were then allowed to develop without further operation until the sixth month, or thereafter, when cortical regions were removed from the second hemisphere. Detailed records (written and photographic) were kept of motor performance, behavior and development; abstracts from representative histories are recorded in the protocols below. Histological studies are being made of the tissue removed at operation, and from the brains after autopsy. These will be reported in detail later when the studies of the animals now living have been completed.

Experimental Data

The normal infant macaque has a relatively high degree of independent motor function at birth as compared with man and anthropoid. All new born monkeys cling unaided to their mothers and suck at the nipple a few minutes after birth; they continue to exhibit these behavior patterns for the first few weeks of life. Although there is considerable variation in motor ability—which generally appears to correlate with the weight and size of the infant at birth—all new born infants placed on a flat surface will promptly right themselves and a few are able to stand somewhat unsteadily and on a broad base. By the second week they can stand and crawl, but still with tremulous uncertainty and they begin to bite at solid food. During the third week progression is more accurate but the grasp reflex and the tendency to cling is still dominant. Shortly thereafter, during the fourth or fifth week, purposeful use of the hands begins. At this age, voluntary release of grip appears, the infants leave the mother, and move about exploring objects and touching them with the face or hands. They do not begin to feed or use the hands or to pick up objects until the middle or end of the second month. In this series, therefore, lesions made during the fourth week of life occurred at a time when voluntary movement was minimal, and when the stereotyped motor performance of reflex grasping and of climbing was still dominant.

Unilateral ablations

In the following experiments, unilateral cortical ablations were made on 5 infant rhesus monkeys, during the fourth week of life. Three of these animals (Expts. 1, 4 and 5) are reported also under *Bilateral ablations* following removal of tissue from a second hemisphere at the age of 6 months or more.

Experiment 1.—Ablation of left motor and premotor areas on 21st day of life; transient contralateral weakness without spasticity; awkward prehension until 2nd operation at 6 months. [Infant series, no. 1]

The subject of the experiment was an infant born in the Laboratory of a *M. mulatta* mother, November 27, 1933. (Mentioned previously in preliminary report as Premotor Series, no. 28[6].) In the third week of life it showed, before operation, marked reflex grasping in all four extremities, together with the ability to climb and to walk slowly and unsteadily.

Operation (Dec. 18, 1933).—On the 21st day of life the left motor and premotor areas were ablated (excluding the face areas, motor and premotor).

Postoperative notes. 1st day.—The animal was well recovered from the operation and walked and climbed surprisingly well. The following differences between the right and left extremities were seen: the left were moved more often and more accurately than the right; there was some weakness of grip on the right, but forced grasping seemed as strong on this side as on the left; the right extremities were slightly more extended than the left. There was no increase in resistance to passive manipulation. It was then returned to its mother, and clung in the normal manner.

9th day.—The infant was again removed from the mother and examined. The motor performance seemed in every way identical on the two sides. There was no postural difference, and the right hand and foot were used as quickly, as often and as accurately as the left. Bilateral forced grasping was still present but less marked than at the previous examination. General motor conduct had become slightly more intricate with the growth of the infant.

56th day.—Forced grasping had disappeared on both sides. Motor performance was

much more highly developed, but still did not reach the degree of skill and accuracy of the adult macaque. With increase in dexterity of the hands for finer movements a difference between the right and left became noticeable. Although general behavior seemed equal on the two sides, on walking, the right arm and leg were occasionally raised higher than the left with the right hand everted and extended; the right hand was not used as often as the left for prehension, and the fingers of the right hand were not used quite as well as those of the left.

6th month.—The above differences were still discernible, and it was noted that the slight overstepping of the right and the preference for the left hand were increased by fatigue. Resistance to passive manipulation was not increased on the right. A second ablation was then performed (See below *Bilateral ablations*, Expt. 1, cont.).

The motor deficit resulting from removal of all the motor regions of one hemisphere in this infant was slight both immediately following operation and as growth proceeded. The changes immediately after the operation consisted of a weakness and tendency to use the affected extremities less than those of the normal side. At the end of six months a slight postural hyperextension and eversion of the extremities were present, together with a tendency to use the normal hand more than the affected one; there was also an awkwardness in manipulating the fingers of that hand. Spasticity did not appear. Neither the degree of paresis, nor the spasticity seen in this animal was at all comparable with that which occurs after a corresponding lesion in the immature macaque or in the adult in which conspicuous and enduring spastic paresis develops following a similar ablation.[5]

The next experiment was carried out to compare the effects of a lesion of areas 4 and 6 with that following ablation of the entire frontal lobe.

Experiment 2.—Ablation of left frontal lobe on 28th day of life; deviation of head and eyes to left, slight weakness of right limbs without spasticity; fine movements of digits still lost at 6 months (2nd operation). [Infant series, no. 5]

The subject of the experiment was a *M. mulatta* born April 23, 1937. At four weeks it still retained its infantile grasping and sucking reactions, much as did the previous animal.

Operation (May 21, 1937).—On the 28th day of life, the entire left frontal lobe was removed under ether anesthesia (*i.e.*, all tissue rostral to the sulcus centralis).

Postoperative notes. 5th hour.—Within 5 hours of the operation the motor status was as follows: the head and eyes were deviated toward the left, there was slight facial asymmetry and the left extremities were moved more quickly and spontaneously than those on the right; rhythmic progressive movements were made equally well on the two sides. Except for head turning, there was little abnormality in posture save that the fingers of the right hand tended to flex and curl under slightly more than those of the left.

30th day.—The deviation of the head and eyes had disappeared; motor coördination had improved and the infant was beginning to use its hands for feeding. It was then to be seen that the left hand was used more quickly and more accurately than the right. There remained, under excitement, a trace of turning of the head and eyes. Thumb sucking, in this as in other animals, was an indication of motor performance: a thumb sucker since birth, this animal sucked only its left normal fingers after the operation; when restrained in this, it attempted to suck the right thumb, but since the right fingers all moved together, it was impossible to place a single digit in the mouth.

During the ensuing four months prior to the second operation, the monkey showed little further recovery. Resistance to passive manipulation was not increased on the operated side.

The motor deficit resulting from removal of the entire frontal lobe in this infant consisted principally of its tendency to use the normal rather than the paretic extremities—particularly in thumb sucking; fine movements of the

affected fingers were less well performed than normal. There was also a slight postural difference between the fingers of the two sides, but no spasticity. The motor performance of the first few weeks was markedly altered because of the deviation of the head and eyes. Indeed, comparison with Experiment 1 indicates that there was no significant difference in motor performance between the two, except for the deviation of head and eyes in Experiment 2, due to inclusion of area 8 in the ablated tissue.

In the next experiment only the motor area (area 4) was removed.

Experiment 3.—Ablation of left area 4 on 26th day of life; slight postural change on right disappearing in 10 days; no other disability; 2nd operation at 6 months. [Infant series, no. 13]

This infant was born of *M. mulatta* parents on May 12, 1937. and developed normally.

Operation (June 7, 1937).—The left motor area (area 4 alone) including face area was removed on the 26th day of life.

Postoperative notes.—As the animal came out of ether, it was noted that, "when it vocalizes and struggles all four extremities are moved spontaneously in contrast to the movement following area 4 and 6 extirpations which is ipsilateral only. The movements of the right extremities are far less accurate and more extended than those of the left."

1st day.—There was some eversion of the right hand and foot, but posture in standing, running and walking was otherwise normal. Forced grasping was slightly more intense on the right than on the left. Spontaneous movements were as numerous and as rapid on the right as on the left side.

10th day.—Motor performance of the two sides seemed equal. Posture was normal, fine movements were well performed with both hands, and the right thumb was sucked as often as the left. Performance at this stage was still infantile in that the animal fed itself by moving its mouth to the food without the use of either hand. From that time on no difference between the extremities of the two sides was detected. Placing and hopping reactions were bilaterally present.

Ablation of the motor area alone in this infant caused only a temporary motor deficit, consisting of a slight inaccuracy of movement on the right, and some postural asymmetry. There was spontaneous movement on the right, which at all times was as great as on the left. Ten days after operation no difference could be detected between the two sides, and thereafter fine movements were as well performed on the right as on the left. Placing and hopping reactions were bilaterally present. The deficit here was much less severe than in those animals in which the premotor area had also been ablated, and it was less severe than in the adult after ablation of area 4, in which paresis, particularly of the fine movements of the hand, persists indefinitely.

It was thought that in the previous types of operation, dissection of the motor regions might not have been deep enough to remove all Betz cells and that functioning motor cortex might remain. For this reason in the next infant, the postcentral gyrus (areas 3-1-2 and 5 of Brodmann), as well as areas 4 and 6 were included in the block removed, care being taken to cut well below the central sulcus.

Experiment 4.—Ablation of left motor, premotor and parietal regions on 18th day of life; weakness, awkwardness and eversion of right extremities without spasticity; residual impairment of digital movements at 7 months (2nd operation). [Infant series no. 4]

This infant *Macaca mulatta* was born August 12th, 1936.

Operation (Aug. 30, 1936).—In the third week of life, the left motor, premotor and parietal areas (areas 4 abc and 3-1-2).

Postoperative notes.—Immediately following operation there was no greater change in the performance of the contralateral extremities than that which appeared in previous experiments after removal of motor and premotor areas alone. No differences were evident between the extremities of the two sides when climbing, but, as in the preceding animals, it exhibited on the right some postural changes, and overstepping when progressing on a flat surface. It had acquired the habit of sucking its thumb, but, after operation, sucked the left thumb only, and that constantly for the next six months. No sensory deficit to touch or pain could be demonstrated. With the appearance of more intricate behavior patterns the motor deficit on the right became more marked; awkwardness of the right hand in picking up objects, occasional overstepping and missing of aim with the right extremities were noted. Resistance to passive manipulation was the same on the two sides. At 7 months the remaining motor, premotor and postcentral regions were extirpated (see *Bilateral ablations*, Expt. 4, cont.).

Ablation of the left motor, premotor and parietal regions in this infant was followed by (i) some awkwardness in the use of the right extremities, (ii) a tendency to use the fingers of the normal hand in preference to those of the abnormal, (iii) overstepping and dysmetria of right extremities—a symptom which increased in severity with the appearance of more intricate behavior patterns. There was no increase in resistance to passive manipulation.

Comparison of the protocols of the present animal and two others with a similar ablation suggested that the infants having postcentral ablations in addition to motor and premotor, showed slightly greater deficit than did those with lesions of areas 4 and 6 alone. The difference is, however, inconsiderable but the overstepping and awkward use of the hands were noted more often when the postcentral regions were also removed.

Experiment 5.—Left hemispherectomy on 28th day of life; slight right hemiparesis without spasticity; deviation of head and eyes toward left; residual tendency to circle toward left and use left hand for skilled acts. [Infant series no. 17]

This infant *Macaca mulatta* born June 29, 1937, showed in the third week of life a little more highly coördinated type of behavior than was present in other infants at this age. Voluntary grasping of objects had appeared and walking and running were fairly rapid, although still executed with less skill than that shown in adult behavior.

Operation (July 29, 1937).—In the fourth week of life the entire left hemisphere was removed under ether anesthesia.

Postoperative notes. 1st day.—By the end of the day walking and eating were well carried out. Movements on the left were quicker and more accurate than on the right. Forced grasping, still present before the operation, was marked on the left and diminished on the right. Groping and clinging were excessive. There was extreme deviation of the head and eyes to the left which was accentuated by excitement or interest.

2nd day.—It could feed and care for itself. Circling was prominent and sensory deficit could be shown by a difference in response to touch of one as compared with the other side of the body, and by the fact that in walking, the right extremities assumed bizarre postures sometimes getting "lost" and tangled in the cage bars. There was no increase in resistance to passive manipulation of either side. The right extremities were often held more extended than the left. A curious cat-like crouching gait developed in this as in another hemidecorticate infant, and all motor progression was slowly and cautiously undertaken.

30th day.—Some circling toward the left remained. The right hand was used less often than the left, the right extremities were occasionally hyperextended with "overstepping" on rapid progression or with fatigue. Placing and hopping reactions were absent on the right. There was no spasticity and motor coördination was in every other way equal on the two sides.

Eight months after operation this motor status was unchanged. The right motor and premotor areas were then removed. (See *Bilateral ablations*, Expt. 5, cont.)

This hemidecorticate infant showed, following operation, a tendency to use the left (normal) hand more than the right, and some hyperextension of the right arm and leg. The right hand could be used for fine movements, but not as well as the left. Movements were slower than is normal, and there was a crouching gait, but no spasticity; deviation of the head and eyes and turning were present throughout the first month, although these symptoms gradually diminished in intensity. Again, differences noted between the effects of different lesions were slight. Comparison of the protocols of this animal and a second hemidecorticate infant with those of animals having smaller lesions indicate that there is a trifle more overstepping in the hemidecorticate and a little longer duration of symptoms than in infants with area 4 and 6 lesions, or in those with the added postcentral ablation.

Bilateral ablations

In the four following experiments the results of bilateral cortical ablations are described. In each instance the first extirpation was made upon an infant monkey during the third week of life; the tissue was removed from the opposite hemisphere at a second operation during or after the sixth month of life.

Experiment 1 (cont.)—Ablation of right motor and premotor areas at 6th month; great increase in motor deficit with spasticity; seriatim ablation of right and left frontal areas in 4th year; increase of spasticity and awkwardness after each operation. [Infant series no. 1]

At the age of three weeks, the left motor and premotor areas had been removed from this infant (see p. 479). At 6 months the residual changes consisted of: a tendency to use the contralateral extremities less than the ipsilateral for fine movements, and a tendency to overreach with the right extremities.

Second operation (May 28, 1934).—At 6 months the remaining (right) motor and premotor areas were removed (Fig. 2).

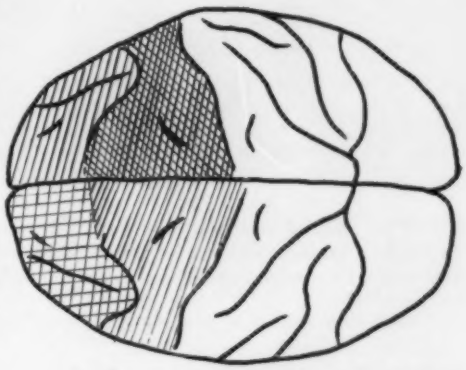

FIG. 2. (Expt. 1.) Diagram of cerebral cortex of *Macaca mulatta* showing the four ablations made on Expt. 1.

Postoperative notes. 1st day.—The motor deficit was great on both sides, but greater on the left than the right. The animal was able to walk and feed itself; all movements were slow, but walking and climbing were well performed. Forced grasping, absent since the second month of life, returned and was greater on right than on left. Voluntary prehension was possible on the right but not, at this time, in the fingers of the left hand. The posture on the left was more in extension than normal and with excitement or fatigue this difference increased and the abnormal movements became exaggerated. The tendency to cling and climb, present in the infant, returned and persisted for many months. The animal walked on a broad base.

1st week.—Improvement in motor coördination was great: running, walking and climbing were well executed, although not as rapidly nor as skilfully as in the normal six-months infant. The left extremities were more extended than the right, and there was some increase in resistance to passive manipulation on both sides. The fingers were not used for feeding although both hands could grasp small objects.

3rd week.—The hands were used in feeding; the tendency to climb and hang persisted and the slight hyperextension and spasticity remained.

7th week.—No change had been observed; forced grasping could still be brought on and at this time the ability to jump long distances and to spring in the air, which later became prominent parts of behavior, were first noted.

8th week.—The protocol reads: "The motor performance has improved markedly. It runs more quickly and moves more accurately. Climbing is performed in the normal way, but performance on a flat surface is now almost normal. There is still a noticeable awkwardness in manipulating fine bits of food which seems to be equal in extent in the extremities of both sides." The animal's ability to groom at this time is shown in Fig. 3.

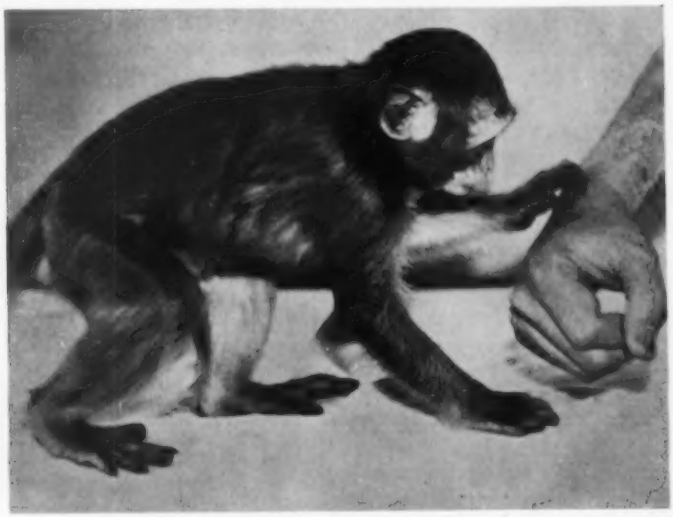

FIG. 3. (Expt. 1.) Infant macaque following bilateral ablation of areas 4 and 6, showing "flea-picking" act (grooming).

This animal was observed in the Laboratory for three years during which time, lacking motor areas in both cerebral hemispheres, it was able to perform ordinary cage activities and to grow and mature. During this time the motor deficit became a little more pronounced.

3rd year.—The following abnormalities were noted: Posture of the extremities in walking and running was "spastic," *i.e.*, extremities were held more rigid, hands and feet were everted, overstepping was seen; all movements were slower than normal; the tendency to cling and climb had remained; in feeding the finger movements were less accurate and less discrete than normal.

Third operation (*Mar. 5, 1937*).—The remainder of the *right* frontal lobe (areas 8-12) was removed (Fig. 2).

Postoperative notes.—Following this procedure the disability in the extremities became much more marked on both sides, but it was greater left than right. The legs became as rigid as poles, and conspicuously everted. The left hand was not used for feeding and the right was used awkwardly and not until the third postoperative week. Turning of the head and eyes, and circling toward the side of the lesion also appeared, presumably due to removal of area 8. All motor acts were carried out slowly and for a time after the operation the animal showed such a high degree of hypokinesia and apparent confusion, that, for several days, it had to be fed by pouring liquids into its mouth.

6th month.—The confusion had entirely disappeared by the end of the ensuing six months, but there had been little improvement otherwise. Climbing and clinging were prominent. Resistance to passive manipulation, especially flexion, was intense at all joints.

Fourth operation (*Nov. 18, 1937*).—The remaining left frontal areas 8-12, were then removed. Following this, the spasticity and tendency to climb and cling were unaltered,

as was posture, but the left hand was used somewhat better than the right; the right extremity, indeed, showed, for a time, no voluntary movement whatsoever, and hypokinesia became extreme. The animal would not move for days after the operation, except when grossly stimulated. It made no attempt to feed or swallow, so that feeding by stomach tube became necessary for a time. During the succeeding 8 months there was gradual recovery and speed of reaction slowly increased. It became able to feed itself and to pick

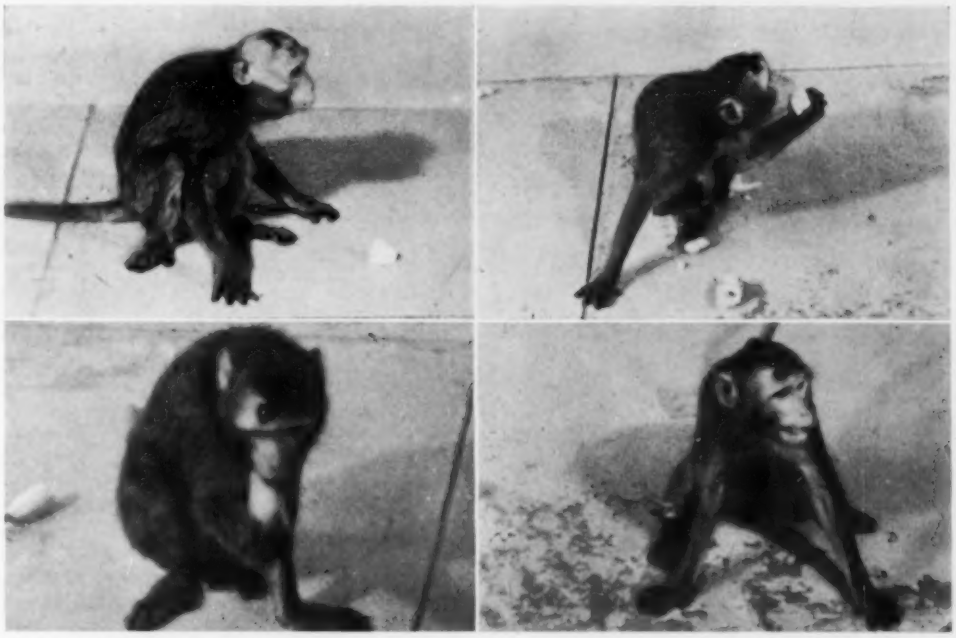

FIG. 4. (Expt. 1.) Enlarged photographs of macaque from moving pictures taken Dec. 4, 1937 after removal of all frontal lobe tissue, showing posture and use of hands.

up objects with either hand (Fig. 4). The spasticity and bizarre posture with rigid extremities remained. All movements were exaggerated and poorly coördinated. This animal is still alive (October, 1938) at the age of almost five years. It is now a mature female in excellent nutritional state and with normal menstrual cycles, able to feed itself and exist in a cage in spite of extreme motor disability. It feeds by bringing its face down to a pan in which food is placed. When excited it springs wildly in the air, usually falling on its back, and for the rest of the time is found clinging solemnly to the bars of the top of its cage.

Extirpation of the remaining motor and premotor tissue from a six-months-old macaque, from which one motor region had previously been removed at three weeks, was followed by marked bilateral increase in motor disability, greater on the side contralateral to the second operation; it consisted of inability to perform fine movements of prehension; there were also postural changes involving hyperextension and eversion of the extremities and moderate increase in resistance to passive manipulation. The subsequent extirpation of the remaining tissue from first one and later the other frontal lobe produced, after each operation, a great increase in the above deficits, together with hypokinesia, deviation of the head and eyes and a seeming apathy and confusion.

Experiment 4 (cont.).—Ablation of right motor, premotor and parietal regions during 7th month; bilateral spasticity and postural changes; "scissors gait" and contractures. [Infant series no. 4]

The changes in motor status ensuent upon ablation of the left motor, premotor and postcentral regions are reported above (p. 481). During the 7th month a residual impairment of the fine movements in the right extremities remained.

Second operation (Mar. 17, 1937).—The second (right) motor, premotor and parietal regions (areas 6a upper part, 4abc, 3-1-2 and 5)were then removed (Fig. 5).

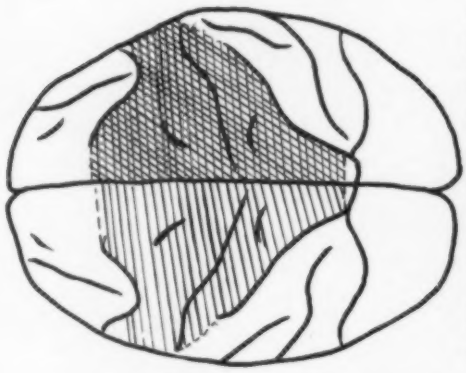

FIG. 5. (Expt. 4.) Diagram of cerebral cortex of *Macaca mulatta* showing areas extirpated in Experiment 4.

Postoperative notes. 1st week.—During the week following operation adequate motor performance developed: running and walking were moderately rapid, but they were executed on a wide base and with greater extension of the left than of the right extremities. There was a slight increase in the tendency to climb and cling, and forced grasping, although difficult to induce, was demonstrable once the animal grasped an object, it had difficulty in releasing its grip. There was a minor increase in resistance to passive manipulation of the limbs and the right hand was used for feeding. The animal tended to "lose" its limbs, particularly those of the left side, so that they became entangled in its bedding and in the bars of the cage. It stopped sucking its thumb, since it was unable to place the thumb in its mouth.

10th day.—Bilateral deficit was still present as it had been during the first postoperative days, but resistance to passive manipulation had increased especially on the left. The hind legs were beginning to be flexed and adducted, necessitating a "scissors" gait, later extreme. There followed a gradual intensification of spasticity and bizarre posture.

2nd month.—The hind legs had become greatly scissored (Fig. 6), the hands were used little in feeding and an enormous exaggeration of all motor response, as in jumping, or in the startle reaction to fear, appeared.

First year.—The notes record a gradual augmentation of the disability due to development of contractures and of an intense degree of spasticity. The animal now (August 1938) climbs and clings rather more than a normal monkey of its age. It walks with exaggeration of all movements and springs enormous distances (6 to 8 feet) having little control over the extent of its motor response. It feeds itself, usually reaching with its mouth for food, although either hand may be used for prehension. Individual movements of the fingers are not demonstrable.

Bilateral ablation of motor, premotor and parietal regions in this animal was followed by a severe motor disability. Although the animal could walk, climb and feed itself, gait and posture were grossly altered. Spasticity was conspicuous together with contracture, scissors gait and great limitation of the movements of the fingers. The disability in this animal and in two other infants (baboons) following the removal of the same areas, was far greater than that which results from the bilateral removal of the motor and premotor areas. The adductor spasm and scissors gait were characteristic of all three of these animals and of no others in this series with lesions elsewhere.

Experiment 6.—Ablation of left motor and premotor areas during 4th week of life; residual slight awkwardness in use of fingers. Right hemispherectomy; bilateral spasticity, forced grasping and circling toward the right. [Infant series no. 7]

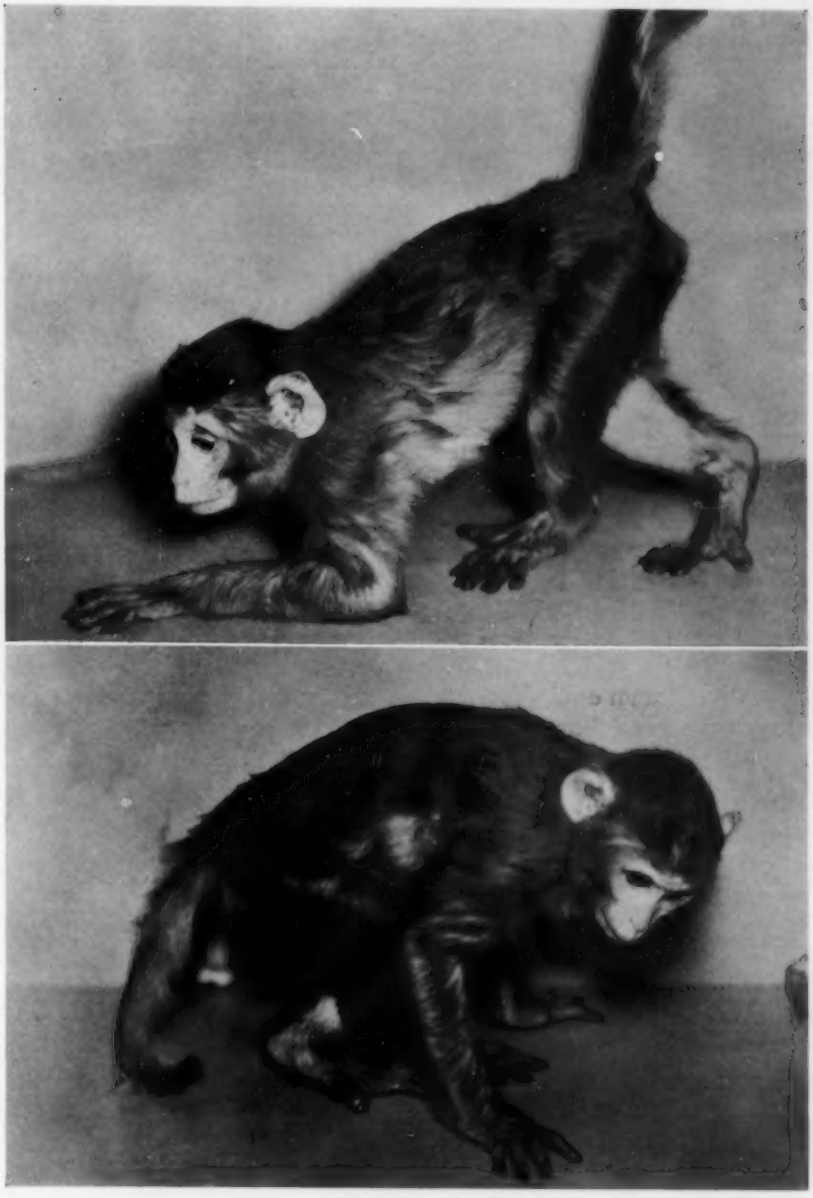

FIG. 6. (Expt. 4.) "Scissors gait" appearing after bilateral ablation of motor, premotor and postcentral regions.

Removal of the left motor and premotor areas from this infant, born April 5, 1935, during the fourth week of life was followed by minimal motor disturbance, such as is described in Experiment 1. A year and a half later the animal showed normal posture and cage behavior with no spasticity and with reflexes equal on the two sides. It tended to use the left hand more than the right and placing and hopping reactions were absent in the right foot.

Second operation. (Sept. 30, 1936).—The right hemisphere was then removed in its entirety under ether anesthesia (Fig. 7).

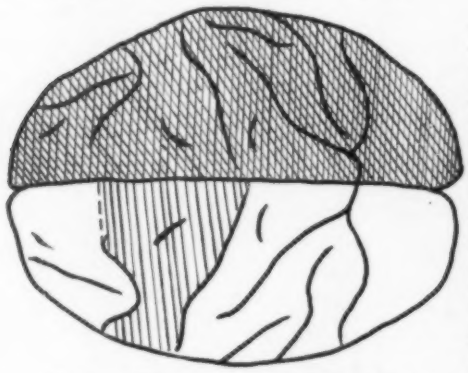

FIG. 7. (Expt. 6.) Diagram of cortex of *Macaca mulatta* showing regions extirpated.

Postoperative notes. 1st day.—The animal was able to right itself and stand and walk. There was bilateral motor deficit, but its behavior was more nearly like that of a hemidecorticate adult than an animal with bilateral motor and premotor area ablation. It circled always toward the right and ate food carried to its mouth by the observer. All four extremities exhibited increased resistance, the left more so than the right, and there was more resistance on flexion than on extension. Forced grasping had also reappeared, and was greater on right than left; all movements were slow and uncertain. Eating was done rapidly and quite automatically, chewing at times continued after all food was swallowed; at other times food was held indefinitely in the mouth. Placing and hopping reactions were everywhere absent.

1st week.—Speed and accuracy of movement were slightly increased, but the type of performance was unchanged. Forced grasping and circling toward the right were so extreme that purposefully directed movement was almost totally prevented. The hands were never used for voluntary prehension.

1st month.—The pattern of motor acts was again unchanged, except that some increase in speed of movements had once more taken place.

The removal of an entire hemisphere after previous ablation of motor and premotor areas was followed by a profound, although not totally disabling, motor deficit. Residual motor function enabled this animal to stand, walk and eat, but spasticity and the loss of coördinate movements of prehension prevented the performance of all the fine motor acts. The deficit was greatest on the side opposite the hemispherectomy and the disability was extreme. The alteration in motor performance in this animal, from which the major part of the remaining cortical tissue was removed when aged a year and a half, was more extreme than in any other animal in this series following any lesion, (Fig. 8). It never regained prehension up to the time of its death six weeks after the second operation. The extremities contralateral to the *second* operation, the hemispherectomy, were the most disabled.

Experiment 5 (cont.).—Left hemispherectomy during 3rd week of life; residual overstepping and awkwardness of right fingers. Ablation of right motor and premotor areas in 6th month; marked bilateral motor deficit, greatest on right, with spasticity, eversion of extremities, and awkwardness in prehension. [Infant series no. 17]

The changes in motor performance ensuent upon left hemispherectomy in this infant are described above (p. 482). Seven months after this first operation there was no spasticity and no postural or motor deficit, except for slight awkwardness in the right fingers, and some overstepping on the right side.

Second operation (Mar. 4, 1938).—The right motor and premotor areas were then removed (Fig. 9).

Postoperative notes. 1st day.—The animal walked and fed itself. Marked deficit was present in the motor behavior of all four extremities. *This was much greater on the right, ipsilateral to the recent operation;* thus the note says: "Yesterday, before the second opera-

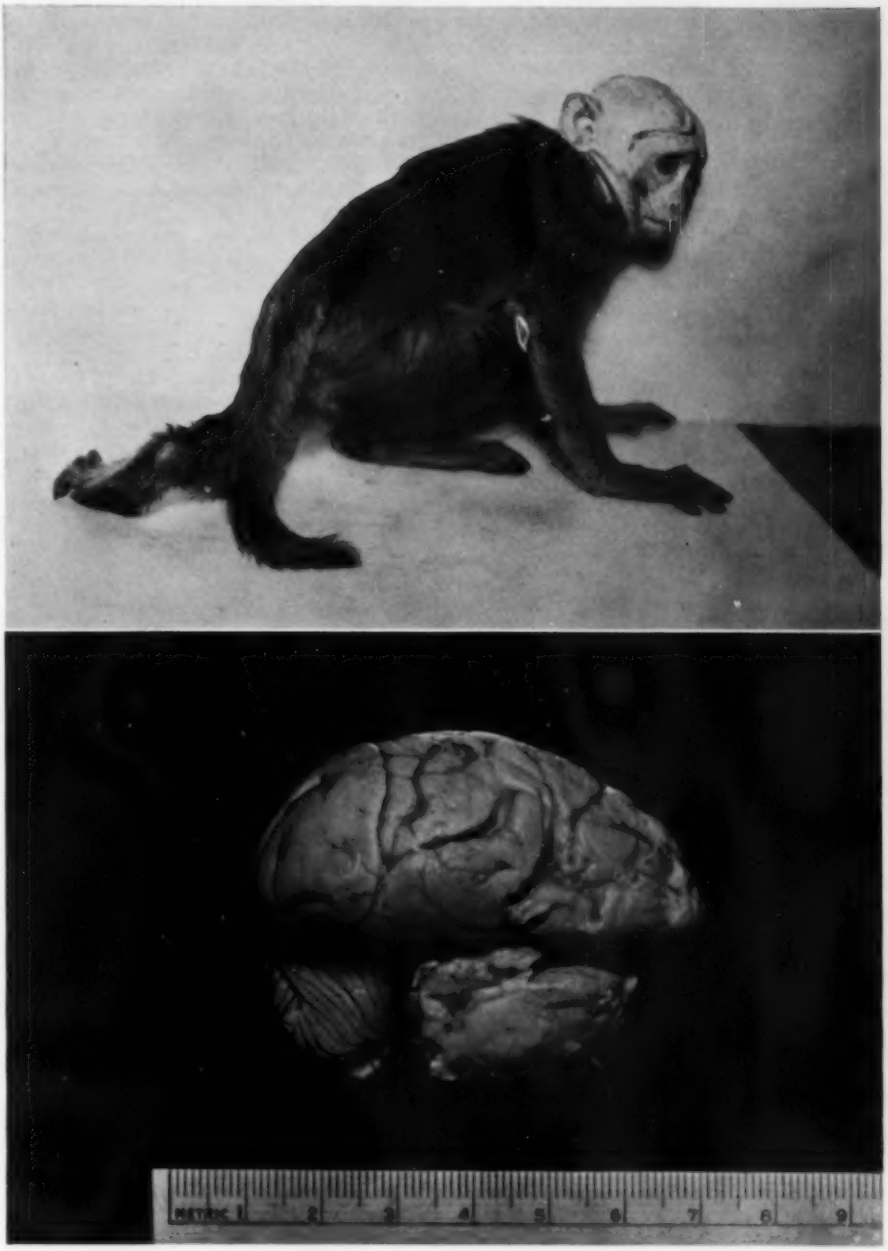

FIG. 8. (Expt. 6.) Characteristic posture of *Macaca mulatta* and brain of same animal photographed at autopsy showing lesion of motor and premotor areas on the left and the hemispherectomy on the right.

tion, the deficit in the extremities due to the left hemispherectomy had practically disappeared. Today this deficit has almost completely reappeared and the animal on first inspection has the appearance of an eight-months infant which has had only a left hemispherectomy. Head and eyes are once more *deviated to the left* and the animal circles to the left, as it did after the first operation. Motor progression is slowly and clumsily done, but the right extremities are more extended than the left. The left hand is used in preference to the right." There was no spasticity, and hopping and placing reactions were absent on both sides.

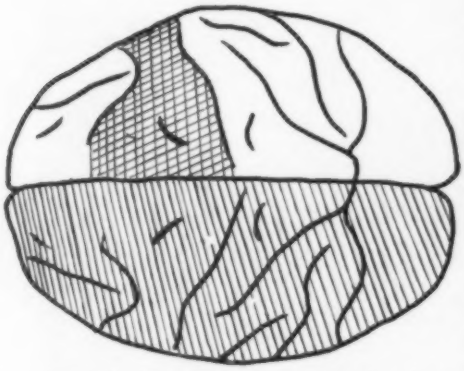

FIG. 9. (Expt. 5.) Diagram showing left hemispherectomy and ablation of motor and premotor areas.

2nd day.—Motor progression had improved but was still slow and incoördinate, the right arm and leg being more extended than the left and less manageable. Feeding was usually done by approximating the mouth to food, but the left hand assisted frequently by shoving and grasping loose bits.

1st week.—The left hand was well used for feeding. Gait was described as "rocking" and on a "broad base" with the tendency to hop, jack-rabbit fashion, instead of running. There was slight increase in resistance to passive manipulation, equal on the two sides.

4th week.—Speed of movement had increased, but posture was still grossly abnormal. The left hand was used in preference to the right but the right could also now be used at times. On both sides, the fingers were moved awkwardly and all together. Deviation of the head and eyes had disappeared.

This animal continues (August 1938) to maintain an adequate existence with two other animals in the cage, being able to run (Fig. 10), feed, climb and play, although obviously lacking a normal smoothness of coördinate motor performance. Chiefly noticeable are the tendency to walk on a broad base with extension, and the eversion of hands and feet. The left hand continues to be more accurate than the right; resistance to passive manipulation is only moderately increased and is equal in the two sides.

Spasticity, increase in extensor posture, and marked limitation of finer finger movements appeared after extirpation of motor and premotor areas secondary to a hemispherectomy. The deficit was greatest on the side opposite the first operation of hemispherectomy. The second operation reproduced the deviation of the head and eyes toward the *side of the first operation*. In this animal, as in the preceding one, the greatest motor deficit was on the side opposite the hemispherectomy. The total deficit was far less than in the previous animal from which the hemisphere was removed as an adult. Thus, degree of deficit in these two animals has specifically to do with age at the time of operation. In an adult, in contrast, severity of paresis is always directly related to the brevity of the interval following operation; and the side opposite the most recent lesion is always the most profoundly affected.

DISCUSSION

It has long been recognized that cortical lesions made on young animals have less effect on behavior than have similar lesions in adults of the same species. In 1866, Vulpian,[12] discussing hemidecortication, advised the use of

young animals since "they stand the procedure better . . . than do adult animals" (p. 677). In 1875 Soltmann[10] found that puppies deprived of one hemisphere develop a highly coördinated motor performance with little difference between movements of the two sides. And in man it has been consistently observed following birth injuries, or other congenital deficiency of brain tissue, that the degree of motor paresis is often small when compared with the effects of a similar lesion in adults. Tsang[11] has recently found that the ability of

FIG. 10. (Expt. 5.) Showing posture of 7 months old *Macaca mulatta* following ablation of left hemisphere and of right motor areas.

adult rats to solve mazes following cortical ablations is proportional to the amount of tissue removed, but that the rat operated upon in infancy will show the same degree of deficit in performance after removal of 50 per cent of cortical tissue, as does the adult following removal of only 7.4 per cent.

The experimental data presented in this paper amply confirm this striking quantitative difference between restitution of motor function in the adult and in the infant animal. Two regions in the central nervous system may be regarded as capable of mediating motor function in the absence of the true "motor" areas: (i) the other areas within the cortex, or (ii) subcortical "centers." At the time of the primary ablation motor function in these infant macaques must be chiefly subcortical, and it might be supposed that in the absence of the higher motor areas these older centers would then develop more complex motor patterns. It is possible that they do, yet the present data indi-

cate that the more complex motor performance of the infant as compared with the adult, which develops in the absence of motor areas, is mediated chiefly through other regions of the cerebral cortex.

In the adult the chief cortical motor projections influencing an extremity originate in the motor and premotor areas of the opposite hemisphere. The ipsilateral motor and premotor areas are known to affect motor performance and since there is also slight but definite recovery after removal of all motor and premotor cortex, contralateral regions other than areas 4 and 6 may also exert some influence. But, since, in the absence of areas 4 and 6, the performance of the adult is little more complex than that of the infant, in which cortical influence is minimal, the effector pathways of the cortex in the adult must be limited chiefly to the motor and premotor cortex; and residual motor performance after their ablation must be due largely to subcortical centers, as in the "thalamic" animal.

The chief motor pathways from the cortex of the young animal also come from the contralateral motor areas. However, in their absence motor performance develops to almost normal limits in the growing and developing animal (Expts. 1, 3 and 6) and ablation of the motor areas from the ipsilateral side will then produce motor deficit about equal on the two sides (Expts. 7 and 8). Thus, in the absence of contralateral "motor" areas, the ipsilateral "motor" regions of the infant become more effective than those of the adult. Similar influence can also be seen in the non-motor regions where tracts from frontal association and postcentral regions of the infant may have an important influence on motor performance (Expts. 1 cont., 5 cont., and 6). The influence of the postcentral regions is obvious from Experiment 4 in which following bilateral removal of motor, premotor and postcentral areas greater motor deficit appeared than in animals with motor and premotor ablations only.

Time of onset of motor function in the cortex

The motor and premotor areas of the three-weeks-old infant clearly participate in reflex motor acts since: (i) their removal results in definite, though slight, alterations in performance; (ii) removal of the motor area alone produces less change; while (iii) removal of other areas, such as the occipital lobes, have at this age no effect on motor status. (The latter observations were made on two infants operated upon for another purpose, and not included in this series.)

However, during the third week of life, motor performance is evidently largely subcortical. It is of simple and limited pattern, chiefly composed of automatic components such as grasping. It is only slightly affected by cortical lesions which in older animals produce greater effect, and, with the later appearance of more intricate patterns of performance, the deficit becomes intensified; that is, as the cortical type of performance becomes dominant, the increase in deficit, though small, is manifest. Stimulation of the motor area in these 15 animals produced motor response in only 9. The responses

differed from those of the adult in that a stronger stimulus was required to produce movement, and the movement was always generalized *i.e.*, the entire limb or side, rather than the discrete response of a finger, or joint, characteristic of stimulation of area 4 in the adult. Soltmann[11] reported these same differences on stimulation of cortices in young and adult cats and dogs.

Physiological evidence indicates that conjugate movements of the eyes and head turning are early under cortical control. In the adult, after lesions of area 8 in the frontal lobe, deviation of the head and eyes, and consequent circling in progression develop. The same result is obtained after lesions in the infant, and, in contradistinction to the results of lesions elsewhere, it is a severe and enduring change which closely approaches the corresponding paresis of an adult. In Experiment 5 the transient head and eye deviation toward the side of the lesion (left hemispherectomy) was reproduced six months later, and *in the same direction*, by extirpation of the contralateral areas 4 and 6 which in the adult have no effect on eye movements.

Anatomical correlations

Since many of the animals in this series are still alive and histological material is not yet complete, a detailed correlation of anatomy and physiology will be reported later. The relation of the development of function with myelinization is still uncertain, although in all vertebrates it is agreed that fully developed motor coördination appears only with myelinization. Artom[1] has observed myelinization in two macaques, one new born and one three weeks of age, and has compared his findings with those of Mingazzini in a baboon of three weeks. In none were the corticospinal tracts myelinated. The present data fit well with two theories discussed at length by Langworthy,[7] namely, that myelinization occurs in proportion to use, and that, as it starts nearest the cell bodies, the shorter axons are complete first. The relatively high degree of functional activity of the cortical eye center as compared with those of the limbs would thus be explained, for shorter tracts in organs such as the eyes which are used early are here involved.

The histological structure of the cortex is consistent with the existence of motor function in postcentral and frontal association areas; for in the postcentral region Betz cells and other large motor cells appear in the fifth layer and in the frontal areas. Area 8 and the caudal part of 9 contain a motor type of cell, although smaller than those of the postcentral areas. In the infant, the cortical layers are less well differentiated as are the individual types of cell, a factor which may be correlated with the lessened specificity of function of the cortex at this age.

Neurological changes

Spasticity. The problem of the development of spasticity or of increased resistance to passive manipulation is of interest. In general, rigidity and spasticity were absent up to 6 months of age after unilateral lesions made in in-

fancy; a second lesion of the opposite hemisphere caused immediate though moderate increase in resistance bilaterally. This gradually increased over a period of months as the animal grew older. The rigidity was extreme, and followed by contractures in three animals having bilateral removal of motor, premotor and postcentral regions, and in the animal with all the frontal lobes of both sides removed. This late development of rigidity may in some way be related to the phenomena fully discussed by Langworthy[8] although appearing at a different age, namely, that young animals (kitten, guinea pig and opossum) when decerebrate, do not develop rigidity, but show extreme hyperactivity and rhythmic progressive movements. Later, at a time which correlates roughly with myelinization, decerebration will produce rigidity in the same species. The hemiplegias of young human infants are not, in general, as spastic as are those of adults, but little is known about the intensity of this factor in relation to age in man.

Posture. The stance and posture of these animals following various extirpations was so constant as to merit mention; their interpretation would be more difficult. Three types were seen: (i) the hemidecorticate infant without spasticity or limb asymmetry walks like a stalking cat, slowly and cautiously, with shoulders low and forelegs slightly bent. (ii) The infant following bilateral ablation of the motor and premotor areas walks on a broad base with hands and feet everted, fingers and toes spread, and with slight overstepping. Additional removal of the frontal association areas accentuates this (Figs. 4 and 10). The animal then walks as if on poles with widely separated and extended legs. (iii) Add the postcentral gyri to ablated motor and premotor areas and a "scissors gait" is produced. Here there is extreme rigidity, with gross adduction and flexion of the hind limbs and some of the fore, although the hands remain everted, fingers spread (Fig. 6).

Reflexes. The absence of detailed notes on reflexes in the protocols of the infants is conspicuous and a result of the difficulty of examination and the equivocality of the results. An infant monkey, when not clinging, is nearly always struggling, so that even with unlimited time and patience, consistent findings would be impossible. Tendon jerks are difficult to evaluate in the adult monkey; in the infant, no significant differences were detected as the result of operation. The changes in reflex grasping could be watched, however, and definitely related to the development of voluntary prehension. The effect on forced grasping of the ipsilateral cortex is far greater in the infant than in the adult. *Placing and hopping reactions* were, in every case examined, abolished by motor and premotor ablation. In one case with bilateral ablation of area 4 alone, placing and hopping reactions still existed.

It is thus evident that the functional organization of motor activity in the central nervous system of the adult monkey may be greatly altered by the early removal of the motor and premotor areas of the cortex; it is clear also that in the absence of areas 4 and 6 other cortical fields may take over, in part, the integration of motor activity. Further study may bring to light the

anatomical and physiological factors which make possible in the infant nervous system this extraordinary reorganization of functional activity.

Conclusions

1. The highly developed and coördinated motor performance which is present in the monkey deprived of motor and premotor tissue in infancy is due to integration from the other cortical regions, namely the frontal association areas and the postcentral regions.

2. The motor deficit under such conditions consists of a loss of the finer movements such as those of prehension.

3. Infantile patterns of behavior, such as reflex grasping, and a tendency to climb and cling are brought out by total ablation of the motor areas and persist indefinitely although voluntary purposeful behavior is also present.

4. Characteristic postures appear with specific lesions. With bilateral extirpation of motor and premotor areas, hyperextension and walking on a broad base appear. On addition of the postcentral gyrus to the above lesion, adduction and a scissors gait ensues.

5. Paresis of conjugate deviation of the eyes following lesions of area 8 is more severe and enduring in the infant, than is the paresis produced by other cortical ablations. It thus resembles more nearly the paresis produced in an adult by a similar lesion. It is suggested that this may be due to earlier myelinization and functional development of these shorter tracts.

6. The concept that specific cortical foci have major functions in specific regions of the body, and in addition a minor influence on many other parts is not new, and applies to the adult cortex, but in less degree than to the infant cortex. The factor which makes possible the enormous difference in degree, however, is still to be explained.

I should like to express my thanks to Drs. J. F. Fulton and C. F. Jacobsen for their advice and encouragement in this investigation, and to Dr. Fulton, Dr. Jacobsen, Dr. Robert Dow and Mr. Robert Malmo for assistance at operations.

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THE SUMMATION OF FACILITATING AND INHIBITORY EFFECTS AT THE MAMMALIAN NEUROMUSCULAR JUNCTION

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DURING progressive curarization, stages are reached in which excitation of voluntary muscle by a given nerve impulse may be either prevented or made possible through the after-effects left by earlier impulses. The nature and the number of these after-effects are uncertain. In the mammal there are three distinct phenomena to be accounted for, namely:

1. *Wedensky inhibition.* While isolated volleys of impulses are still able to excite the muscle, repeated stimulation of the nerve may at certain rates lead to a state of more or less complete junctional block. At low frequencies (6 to 600 per min.), the muscle responds more strongly to the first volley than to any following. Each volley of the series, whether transmitted or blocked, leaves an inhibitory after-effect which lasts at least 10 seconds. The higher the frequency of stimulation, the more profound is the final level of inhibition reached; but at tetanizing frequencies two or more volleys may be transmitted before any evidence of inhibition appears.

2. *A brief phase of facilitation.* When isolated volleys are blocked, two in rapid succession may still excite. The facilitating after-effect of the first volley is maximum at about 3 m.sec. (Bremer and Homès, 1932) but persists in some degree for 40 or 50 m.secs. Tetanic stimulation of the nerve, however, evokes only an initial twitch-like contraction. Junctional block then returns and remains as long as stimulation is continued at the same frequency.

3. *A second, more prolonged, phase of facilitation.* After tetanic stimulation of the nerve is stopped, the muscle is found to respond to single volleys timed a few seconds apart. This post-tetanic recovery is still demonstrable when curarization is so far advanced that the conditioning tetanic stimulus, however prolonged, fails to elicit any visible contraction (Boyd, 1932). For brevity, the underlying processes responsible for these three phenomena will be designated respectively I, F_1 and F_2, although it is not certain that the two last are distinct. Rosenblueth and Morison (1937) have suggested that F_1 is a summation of two or more quanta of acetylcholin (ACh), released at the same nerve ending; I, a diminution in size of the later quanta of a series, such that they become inadequate to excite even by summation; and that F_2 is a mobilization of potassium, released at the nerve endings.

None of these hypothetical processes has been definitely identified. In an earlier paper (Maaske, Boyd and Brosnan, 1938) evidence was given indicating that F_1 is not a summation of quanta of ACh. Brown and von Euler (1938) hold that F_1 and F_2 are identical, the former being the mobilization of K ions

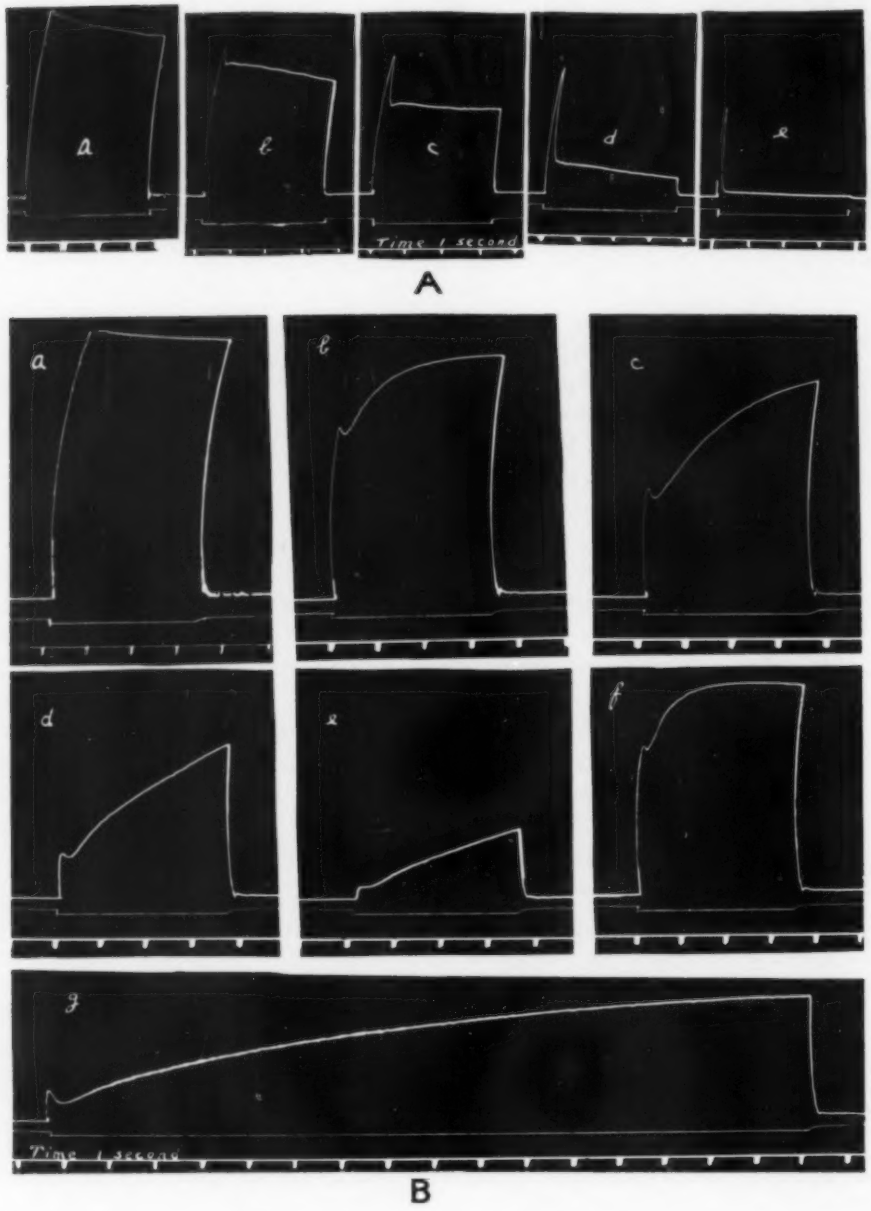

FIG. 1. A, dog, 12.6 kg., nembutal. Contractions of tibialis anterior in response to stimulation of motor nerve at frequency of 80 per sec., for successive 4-second periods. a, normal; b to e, during progressive administration of 21 mg. of crude curare.

B, dog, 15.9 kg., nembutal. a, normal tetanus; b to e, during progressive administration of 9.2 gm. of $MgSO_4$; f and g recorded at same stage of depression as d. Frequencies, a to e, 80; f 120, g 40 per sec.

at the motor end plate by a single impulse, and the latter the same effect magnified by the arrival of a train of impulses in rapid succession. Brown and von Euler offer no explanation for the fact that the two phases of facilitation are separated in time. If the total mobilization of K ions continues to increase during tetanic stimulation of the nerve, the facilitating effect becomes masked, after the first two or three volleys, by some inhibitory factor; and the second phase of facilitation must then be accounted for by assuming that the inhibitory factor subsides with relative rapidity during rest, allowing facilitation to become unmasked again.

Certain facts appear to support this interpretation. Lubinska (1935) observed that during the progressive administration of a magnesium salt the muscle response to single volleys became weaker. When it had failed entirely, continued stimulation of the nerve at a frequency of 27 per sec. evoked a tetanus, gradually built up but well sustained. There was also a post-tetanic return of the single twitch response, maximum at first and subsiding over a period of several minutes. The entire sequence of effects suggests the continued summation of a single facilitating factor, removed during the post-tetanic period by some relatively slow process. In the paper referred to above (Maaske, Boyd and Brosnan, 1938), we showed that the facilitating after-effect of a single volley runs the same time course under Mg as under curare. The inhibitory effect, however, is, under Mg, comparatively brief and feeble. The inference is obvious that under Mg, F_1 can be summated continuously throughout an extended series of volleys; and that under curare the discontinuity between the two phases of facilitation may be only apparent, and due to masking by I.

This paper presents some further observations on the course of junctional facilitation, both under curare and under Mg. It will be shown that under curare, facilitation is present, but masked, during the period of Wedensky inhibition. On the other hand, it will be shown that the building up of a tetanus under Mg is not continuous; it takes place in two stages, for which two distinct processes may be responsible.

PROCEDURE

Dogs and cats were used, anesthetized with nembutal (45 mg. per kilo). The right leg was immobilized by drills through the tibia. Contractions of *m. tibialis anticus* were recorded on smoked paper, the muscle ordinarily being made to pull against a rubber band; but for the tetani shown in Fig. 1 a steel spring myograph was employed. The sciatic nerve was sectioned. All stimuli, except as otherwise stated, were applied to the peroneal nerve through shielded platinum electrodes, and were initially adjusted to a strength just above maximal for the motor fibers. Tetanic stimuli were delivered from a Harvard coil, or, when varied frequencies were desired, from a neon-tube circuit. The latter also served for test stimuli repeated at intervals of 5 to 10 secs. The desired stage of junctional depression was induced and maintained by slow inflow, either of $MgSO_4$, $7H_2O$, in 6.7 per cent solution, or of crude curare, 0.1 to 1.0 per cent, from a burette connected to the left femoral vein. Eserine (physostigmine salicylate) was administered by the same route. In certain experiments the left iliac artery was sectioned and tied in order to permit injections of ACh or of KCl solutions through its central stump into the lumen of the aorta. In the experiments with curare artificial respiration was employed; with Mg it was not necessary.

Results

1. *Responses to tetanic stimulation of the nerve.* (a) *Curare.* Figure 1A (b to e) shows a series of tetani, each of 4 secs. duration, recorded during progressive curarization. The effects shown were described by Hofmann (1903) and these graphs are presented merely for comparison. The maximum tension is reached very early and is followed by Wedensky inhibition, which becomes more and more nearly complete as curarization deepens. The initial rise is meanwhile reduced somewhat in height, but its time course does not change appreciably. While the tetani shown were all recorded with a uniform frequency of stimulation of 80 per sec., the same general form of record is maintained with any frequency from 20 to 120 per sec. At any given stage, however, an increase of frequency improves the initial response, while the after-depression becomes more profound.

(b) *Magnesium.* Figure 1B shows a series of myograms recorded under conditions identical with those of Fig. 1A, except that Mg was substituted for curare. There is here also an initial abrupt rise of tension, followed by partial relaxation. The relaxation, however, is incomplete and transient, being recorded merely as a notch on the ascending portion of the myogram. It is followed in turn by a secondary rise which transcends the first.

Until the secondary ascent begins, these tetani are apparently identical with those of the curarized preparation. With increasing dosage of Mg the primary rise is reduced in height, but its time course does not change appreciably. The time course of the secondary rise is altered, the slope becoming more gradual. Figure 1B, *g*, shows such a secondary rise continuing for 15 secs. After the initial response has been completely suppressed by Mg, a feeble de-

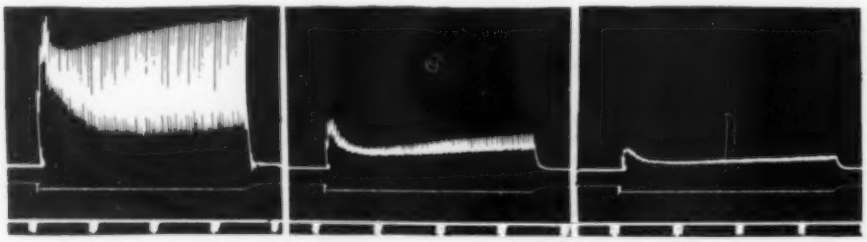

FIG. 2. Same preparation as in 1 B. Responses to stimulation of nerve at frequency of 20 per sec., during progressive administration of $MgSO_4$.

layed tetanus can still be built up by prolonged stimulation of the nerve. At any stage prior to this, an increase of stimulation frequency has the following effects;—a strengthening of both the primary and secondary responses, a steeper ascent for the latter, and a reduction, both in width and depth, of the notch separating them (compare *d* and *f* in Fig. 1B).

We have observed a notch, similar in magnitude and position to those shown in Fig. 1B, in myograms recorded from animals under nembutal alone. In these instances, however, as in those noted by Hofmann (1903) using ani-

mals under deep ether anesthesia, the notch was present only with relatively low frequencies of stimulation and disappeared with an increase of frequency. When the effects of nembutal and Mg are combined, the notch is present at all frequencies up to 120 per sec., although it does undergo the changes described above. A similar notch appears in some of the graphs of Lubinska (1935) although it is left without comment. At a frequency of 20 per sec., the secondary rise is barely perceptible, and never reaches the height of the primary. This type of response resembles, more nearly than any obtained with higher frequencies, a sustained Wedensky inhibition (Fig. 2).

The general form of tetanus shown in Fig. 1B is retained after Mg has completely suppressed any visible response to an isolated volley. Since the Mg block is reversible by the agents which are antagonistic to curare (Brosnan and Boyd, 1937) both components of the tetanus must involve a recruitment of units in the muscle rather than in the nerve. Superficially, the effect resembles that of small doses of eserine. Cannon and Rosenblueth (1937) find a similar "plus-minus-plus" sequence in the response of the nictitating membrane, in lightly eserinized cats, to tetanic stimulation of the preganglionic sympathetics. These authors attribute the "minus" phase to accumulation of a depressing excess of ACh, and the second "plus" phase to a fall in concentration of ACh resulting from an assumed reduction in size of quanta. Such an explanation might equally well apply to the observations of Briscoe (1936) whose myograms, also recorded from eserinized cats, closely resemble those shown in our Fig. 1B.

Under eserine, however, the transient depression is magnified by an increase in the frequency of stimulation (Briscoe, 1936). This is of course to be anticipated if an excess of ACh is the cause. Under Mg, as noted above, increase of frequency has just the opposite effect. For this reason, the notch in our myograms can hardly be attributed to the paralytic action of excess ACh. Moreover, the phase of depression in a tetanus recorded under eserine is abolished after small doses of Mg (Fig. 3).

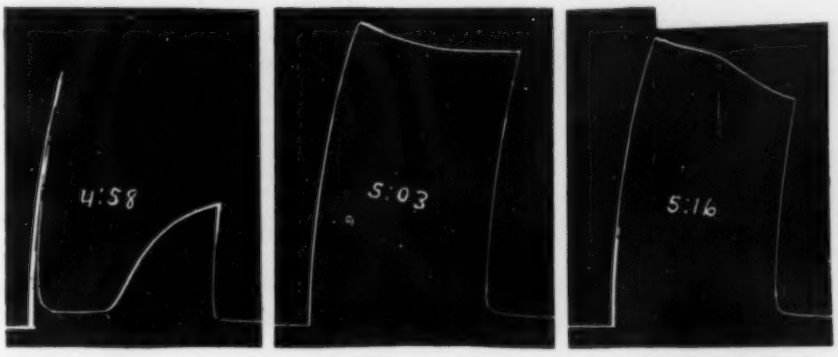

FIG. 3. Dog, 8.8 kg., nembutal. Responses during three 4-second periods of stimulation of nerve, frequency 80 per sec.; at times indicated. Eserine (4.4 mg.) at 4:55. Same dose repeated at 5:11. $MgSO_4$ (5 cc. of isotonic solution) at 5:00. Same dose repeated at 5:13.

It seems probable that the initial response to tetanic stimulation, under Mg, is due to F_1, the same factor which is responsible for the brief phase of facilitation under curare. The notch which follows may mean either the exhaustion of F_1 or a transient masking by I. Similarly, the secondary rise may be due either to a second facilitating factor, requiring prolonged summation to become effective, or it may be due to continued building up of F_1. Obviously, under Mg a sustained decline in size of quanta of ACh either does not take place, or, if it does, there is no resulting impairment of junctional transmission.

2. *Post-tetanic effects.* We have previously reported (Boyd and Brosnan, 1936) that facilitation, following a given tetanus, lasts about as long under Mg as under curare; and that in both conditions the degree and the duration of the recovery vary with the number and frequency of the conditioning volleys. It seems probable, therefore, that the underlying factor (F_2) is the same under Mg as under curare.

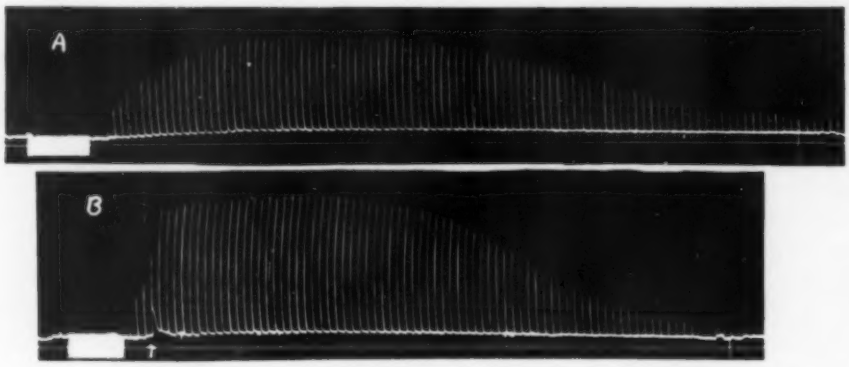

FIG. 4. A, cat, 2.7 kg., nembutal and curare. B, same preparation, after 2 mg. each of eserine and atropine, with additional curare to restore original state of block. Single test stimuli at 8-second intervals throughout, tetanic stimulation (Harvard coil, 1 minute) at signals. At arrow (B) 5 mg. of acetylcholin in 1 cc. saline injected into right iliac artery.

(a) *Curare.* Figure 4A shows a typical post-tetanic facilitation, lasting for 10 mins. The conditioning tetanic stimulation, continued for 1 min., fails to evoke a visible response. The first post-tetanic twitches are relatively feeble, but become progressively stronger until a maximum is reached in about 2 mins. after which there is a more gradual decline. The rising phase of the facilitation curve might be due either to delayed development of F_2, or to its gradual unmasking as I subsides. The latter hypothesis is supported by several observations.

First, the earliest twitches are weaker after a prolonged than after a short series of conditioning volleys. Increasing the number of the latter prolongs not only the total period of facilitation, but also the delay before the maximum is reached. Following tetani of only 1 or 2 secs., the rising phase of the facilitation curve may be so brief that the test stimuli must be timed only 1 or 2 secs. apart in order to demonstrate it at all. The rising phase is briefer, in the tibialis

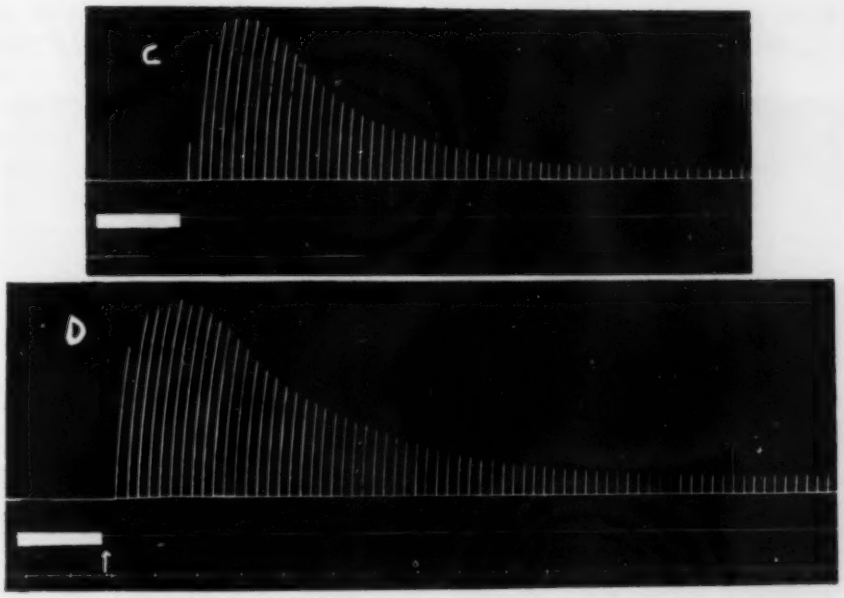

FIG. 4. (continued). C and D, dog, 11.5 kg., nembutal and curare. Single shocks to nerve at 8-second intervals throughout, tetanic stimulation (Harvard coil, 1 min.) at signals. At arrow (D) 3 cc. of 4 per cent KCl injected into right iliac artery.

and also in the tongue of the dog, than in corresponding muscles of the cat; but it can always be demonstrated with suitable spacing of the single test shocks.

Second, a series of post-tetanic twitches is temporarily suppressed during a second period of high-frequency stimulation. Afterward, however, the twitches reappear and become stronger. This is illustrated in Fig. 5C, the

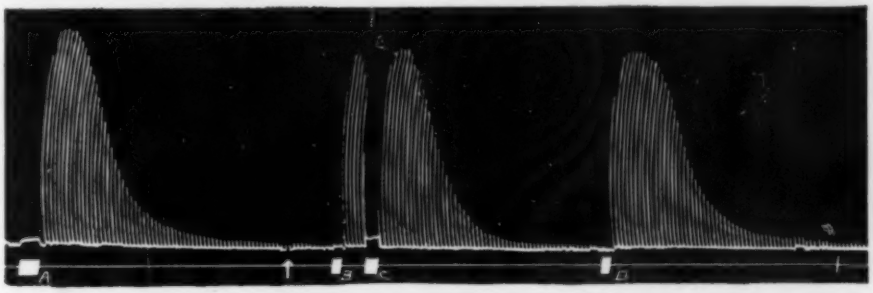

FIG. 5. Dog, nembutal, curare. Single shocks at 7-second intervals applied to nerve throughout. A and C, tetanic stimulation (Harvard coil) through steel needle electrodes in muscle; B and D, tetanic stimulation through a second pair of electrodes on nerve.

suppression being due in that instance to a weak tetanic stimulation through electrodes on the muscle; but the same effect can be produced by stimulation of the nerve trunk.

Third, the post-tetanic recovery becomes briefer and less complete as the interval between test stimuli is shortened. This is shown in Fig. 6A. The op-

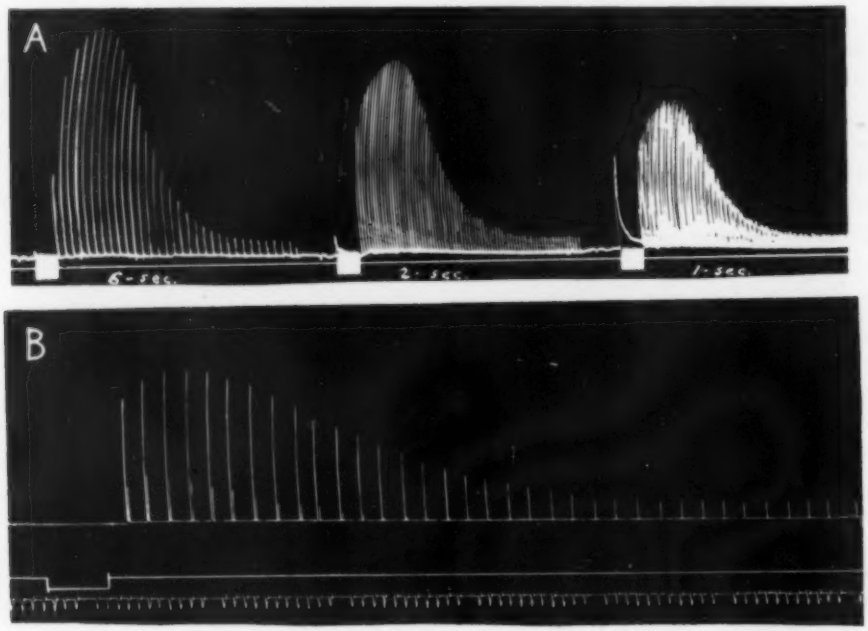

FIG. 6. A, cat, nembutal, curare. Three periods of tetanic stimulation of nerve (Harvard coil, 15 sec.) indicated by signals. Frequency of post-tetanic single shocks 10, 30, and 60 per min., in order given.

B, cat, nembutal, curare. At signal, tetanic stimulation of nerve, 100 per sec., for 30 secs. This followed by paired stimuli 1 sec. apart (interval between pairs 10 secs.) throughout remainder of record.

timum interval between single test shocks is greater than 10 secs. The response to each volley of impulses evidently is inhibited through the after-effect of the preceding volleys, unless the interval is long enough to allow the inhibitory effect to subside completely. The relation is brought out more clearly in Fig. 6B, which shows pairs of twitches 1 sec. apart with a 10 sec. interval between pairs. The second twitch of each pair is much weaker than the first. The first volley of each pair thus leaves an inhibitory after-effect which runs its course against a background of sustained facilitation. It seems certain, therefore, that F_2 and I can exist together without mutual extinction, the latter dominating while it is present.

Fourth, under Mg the post-tetanic facilitation is not delayed. This is clear from the graphs shown by Lubinska (1935) and confirmed by us in (b) below The difference between the "curare" curve and the "Mg" curve may be readily explained on the basis of an absence of masking under Mg.

We have no theory to offer concerning the identity of I, nor can we explain why it is so much more powerful and prolonged under curare than it is under Mg. In a previous paper (Maaske, Boyd and Brosnan, 1938) we questioned

the assumption of Rosenblueth and Morison (1937) that I is a reduction in size of quanta of ACh. Some other hypotheses can with more certainty be excluded.

The rising phase of the recovery curve is not due to local stimulation fatigue of the nerve, which might be expected temporarily to reduce the number of motor fibers excited. The same type of recovery curve is obtained when two pairs of electrodes are used, one for single test shocks and the other for tetanizing. The two may be placed at different levels on the nerve, or one pair on the nerve and the other on the muscle. Tetanic stimulation through electrodes on the muscle is followed by a return of the response to single shocks applied to the nerve. Under these conditions, the tetanic stimuli may be made so weak that the muscle shows only a very feeble direct response, or even none at all. Yet powerful post-tetanic twitches appear (Fig. 5A). Evidently, therefore, the intramuscular nerve fibers have a threshold lower than that of the muscle, and under the conditions described may be selectively stimulated to produce effects identical with those of stimulating the nerve trunk. Guttman, Horton, and Wilber (1937) failed to obtain post-tetanic enhancement or facilitation on direct stimulation of the curarized frog's gastrocnemius; but they also failed, as did Boyd (1932) to obtain it from stimulation of the nerve in the same preparation.

Feng (1937) describes a similar delay in the appearance of facilitation following tetanic stimulation of the nerve in a partially fatigued preparation. He

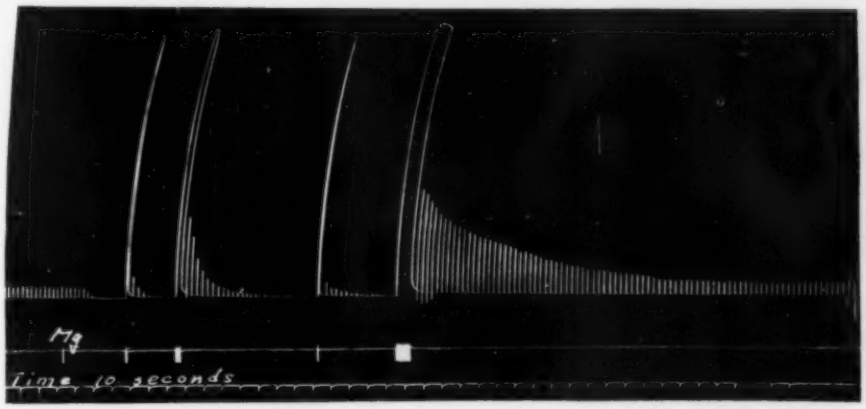

FIG. 7. Dog, nembutal and $MgSO_4$. Single stimuli to nerve at 4-second intervals throughout record. Mg, final dose of $MgSO_4$. Later signals, tetanic stimulation of nerve (Harvard coil) for 1, 3, 1, and 10 secs.

ascribes the delay to the paralytic action of an excess of ACh, and the facilitation itself to the same substance, acting after the depressing excess has been removed. It seems unlikely that ACh can remain undestroyed for so long a time after its release. In the curarized preparation, if ACh be injected into the iliac artery during the rising phase of a recovery curve, the smallest effective

dose potentiates the twitch responses instead of depressing them (Fig. 4B). KCl similarly administered also has a potentiating action (Fig. 4D). The delayed appearance of facilitation is therefore not due to the presence of a depressing excess either of ACh or of K.

(b) *Magnesium.* Under Mg the post-tetanic twitches are maximum immediately after a tetanus (Fig. 7). The decline may begin at once, or after a series of uniform maximum twitches, depending on the number of the conditioning volleys. The post-tetanic recovery and the secondary component of the tetanus itself (see section 1, b, above) are evidently made possible by the same facilitating factor, reaching its maximum development during the tetanus and persisting for some time afterward. With increasing dosage of Mg, a stage is reached at which no post-tetanic recovery is demonstrable; but at this time a feeble, delayed contraction still appears *during* high-frequency stimulation of the nerve. As pointed out above, the effects under curare disappear in the reverse order. Post-tetanic facilitation, under Mg, is not suppressed by a second period of high-frequency stimulation of the nerve; nor is its course appreciably affected by changes in the frequency of the single test shocks.

Summary

1. During neuromuscular depression, produced in the mammal either by curare or by Mg, tetanic stimulation of a motor nerve results in junctional facilitation. This appears in two phases. The first is the latent addition studied by Bremer and Homès (1932). The second, much more prolonged, has been described by Boyd (1932, curare) and by Lubinska (1935, Mg).

2. Under curare, the two phases are entirely separated in time by a period of Wedensky inhibition. During this period a facilitating factor is present, but is masked by the inhibitory factor. The two can coexist without mutual extinction.

3. The inhibitory factor is not a depressing excess of acetylcholin nor of potassium; nor is it a local change affecting the nerve at the site of stimulation. It is far more powerful under curare than under Mg.

4. Under Mg, the two phases of facilitation overlap in time. The only evidence of discontinuity is a partial and transient relaxation which appears shortly after the beginning of a tetanus.

5. Demonstration of the masking effect mentioned in (2) supports the hypothesis of Brown and von Euler (1938) that both phases of facilitation are due to a single factor. It is not yet certain, however, that the separation between the two phases is entirely due to masking.

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A FURTHER STUDY OF THE CROSSED PHRENIC PHENOMENON

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SCHIFF (1894) and Porter (1895) showed that severance of a phrenic nerve in dogs or rabbits results in respiratory contractions of the contralateral hemidiaphragm paralyzed by a spinal semisection on the same side at or above C3. In a previous publication from this laboratory (Rosenblueth and Ortiz, 1936) control experiments on the Schiff-Porter crossed phrenic phenomenon were reported, which led to the conclusion that the appearance of the crossed diaphragmatic contractions upon section of the active phrenic is not due to relative asphyxia or to changes in the afferent nerve impulses set up by the respiratory movements, but that the direct cause of the phenomenon is the severance of the motor fibers in the phrenic. This conclusion entailed the postulation of properties of nerve cells different from that of conducting nerve impulses and unparalleled in any other known experimental conditions. The present study was undertaken to obtain further controls which would support or invalidate this conclusion and its unexpected corollaries.

METHODS

Rabbits and cats were employed. The acute experiments were usually performed under dial anesthesia (Ciba, 0.55 to 0.6 and 0.6 to 0.75 cc. per kg., respectively, intraperitoneally). In some of the rabbits intravenous urethane supplemented the dial; in a few instances urethane alone was given. In the early experiments the diaphragmatic contractions were recorded as described by Rosenblueth and Ortiz, by attaching serrefines connected to recording levers via threads and pulleys to the two diaphragmatic domes just lateral to the tendinous center, after opening the abdomen. Contractions of the diaphragm appear in such records as downward excursions of the kymographic tracing.

In later experiments it was found that Head's slips, which attach to the xyphoid cartilage in the rabbit, provide a more accurate and simpler index of diaphragmatic activity. A midline section of the xyphoid cartilage was made. The muscle was separated from the bony part of the xyphoid process and this bone was cut. Quite independent tracings of the activity of each half of the diaphragm were obtained by attaching the serrefines to the freed fragments of cartilage. In cats, although Head's slips are not as developed as in the rabbit, a similar preparation yielded equally satisfactory results. In the records obtained by this procedure diaphragmatic contraction is denoted by upward excursions of the tracing. For the application of reversible ether blocks the sterno-mastoid muscle was cut at its lower insertion, thus permitting a clear exposure of the phrenic nerve down to C7. A small piece of cotton soaked with ether was then placed on the nerve and removed as soon as the block was complete.

Alternating or direct current was applied to the phrenic for blocking purposes by means of shielded silver electrodes placed between C6 and C7. The component to the phrenic from C7 was eliminated by cutting this nerve at its emergence from the vertebral column—*i.e.*, centrally to the phrenic. The alternating current used was faradic induction shocks from a Harvard coil with 5 volts in the primary circuit. Direct current was obtained from a battery, the intensity being regulated by a potentiometer and measured by a voltmeter. Afferent stimulation of the median, the vagus or the saphenous nerves was faradic, through shielded silver electrodes, after cutting the nerves peripherally. Asphyxia was produced either by attaching to the tracheal cannula a rubber balloon containing nitrogen or expired air, or by occluding the cannula.

The operations which were carried out on some of the animals previous to the acute experiments were made aseptically under ether anesthesia. Other details of the methods employed in particular instances will be found in the corresponding sections below.

Results

Animals with a previously cut phrenic nerve. The purpose of these experiments was two-fold: first, to see whether crossed contractions would appear when the spinal semisection was performed several weeks after cutting the phrenic; and second, to investigate the influence upon the phenomenon of the functional connection of the cut nerve with some structure other than the diaphragm. Accordingly, in 19 rabbits and 9 cats, one phrenic nerve was cut below C7 and its connection with that nerve was severed. The freed central end of the phrenic was then sutured either to the peripheral end of the cut cervical sympathetic, or, more frequently, to the sterno-mastoid muscle, denervated by section of the spinal accessory nerve. One to 25 weeks later the animals were anesthetized with dial, a spinal semisection at C2 contralateral to the previous section of the phrenic was performed, the abdomen was opened and the diaphragm was either observed directly or, more commonly, hooked up for recording in the usual manner. The effects of section of the previously cut phrenic and of the vagi were studied. Regrowth, when present, could be detected by activity in either the pupil or the sterno-mastoid, coincident with the respiration.

The results are summarized in Tables 1 and 2. In the columns marked *Re-*

Table 1

Operated Rabbits

Animal No.	Time after operation (weeks)	Regrowth	Results of semisection	Results of cutting phrenic	Results of cutting vagi
1	1	0	++		
2	2	0	++		
3	4	0	++		
4	4	0	++		
5	5	0	++		
6	6	0	++		
7	13	0	0	0	++
8	22	0	++		+
9	24	0	++		
10	13	+	0	0	+
11	13	+	0	0	0
12	13	+	+	+*	+
13	24	++	+		
14	13	+++	+		++
15	13	+++	0	0	0
16	20	+++	+?	Sl. +*	++
17	24	+++	++	0	++
18	24	+++	0	+**	++
19	24	+++	0	0	0

* The section of the regrown phrenic followed section of the vagi.

** The section of the phrenic was incomplete; later completion led to no further change.

Table 2

Operated Cats

Animal no.	Time after operation (weeks)	Regrowth	Results of spinal semi-section	Results of cutting phrenic	Results of cutting vagi
1	25	0	+	+	+
2	23	0	0	0	+
3	23	0	++		
4	16	0	+++		
5	23	+	0	0	+
6	20	+	++	+?	++
7	19	+	+++		
8	18	++	+	0	
9	16	++	0	0	+

growth, O stands for no detectable functional connections of the anastomosed phrenic; the + signs indicate slight, medium or marked functional regrowth. In the columns marked *Results of semisection* the + signs denote crossed contractions of the diaphragm immediately after semisection—*i.e.*, the hemidiaphragm on the side of the semisection did not stop breathing; O stands for complete paralysis of the diaphragm. The columns marked *Results of cutting phrenic*, or *vagi*, indicate the changes in the magnitude of the contractions of the crossed hemidiaphragm—*i.e.*, of the side ipsilateral to the cord semisection, with intact phrenic—upon section of the anastomosed phrenic or the vagi. The sign O stands for no detectable change and the + signs denote either the appearance of crossed contractions, if the diaphragm was previously paralyzed, or the increase of pre-existing crossed contractions.

The following results deserve emphasis. (a) With two exceptions (rabbit 7 and cat 2) in the animals in which there was no regrowth, spinal semisection elicited prompt marked crossed contractions. (b) In 7 out of the 15 animals with regrowth, spinal semisection did not elicit crossed contractions; in 4 of these animals a crossing occurred later. (c) Up to 24 weeks after cutting the phrenic, spinal semisection may lead to immediate crossing (rabbit 9, cat 1). (d) Immediate marked crossed contractions may appear upon spinal semisection even when good functional regrowth of the cut phrenic has taken place (rabbit 17, cats 7 and 8). (e) Section of the regrown phrenic (incomplete, rabbit 18) may lead to crossing. (f) Section of the vagi may cause crossing after the phrenic has been cut, even though there has been no obvious regrowth (rabbit 7, cat 2), or when such regrowth is present (rabbit 10, cats 5 and 9).

Direct electrical stimulation of the respiratory center or the respiratory tract above C3. Five cats were tested. The results were clear and consistent. Recording from the diaphragmatic domes or from Head's slips was attempted, but the passive movements of the diaphragm transmitted via the chest from contractions of the neck muscles were as a rule confusingly prominent. Visual observation of the diaphragm after wide opening of the abdomen was, therefore, more satisfactory.

The following protocol is typical of the procedure followed and the results obtained. Cat, anesthetized with dial (0.65 cc. per kg. intraperitoneally). Tracheal cannula inserted. Vagi, cervical sympathetics and depressors cut in the neck. Carotids ligated and spinal accessories cut. Cervical nerves C3 toC7 cut peripherally to the phrenics, on both sides. Complete transection of the spinal cord immediately below C7. Left semisection of the cord at C3. Animal breathing only with its right diaphragm; artificial respiration now applied. Cerebellum removed. Midline longitudinal section of the medulla and cord from the upper part of the 4th ventricle to C2. Left semisections at the upper and lower limits of this midline incision and removal of the segment isolated by these sections. Slight compression of the vertebral arteries throughout these procedures to control hemorrhage, when necessary.

Stimulation of either the right respiratory center (electrodes applied to the medial surface of the sectioned medulla just above the tip of the calamus scriptorius; coil distance about 10 cm.) or of the right respiratory tract (electrodes applied to the lateral surface of the cord at C1 or C2; coil distance about 8 cm.) caused marked contractions of the right hemidiaphragm with no involvement of the left side. The right phrenic nerve was then cut. Similar stimulation elicited now strong contractions of the left hemidiaphragm; the right side was of course paralyzed. Completion of the semisection of the cord at C3—*i.e.*, complete transection at that level—abolished the diaphragmatic responses, thus proving that the contractions of the left hemidiaphragm had not been elicited by spread of the stimuli to the left respiratory tract below C3.

Reversible alternating-current or direct-current blocks. Rosenblueth and Ortiz (1936) showed that reversible blocks of the active phrenic after a high spinal semisection, produced by applications either of direct current or of ether, resulted in respiratory movements of the previously paralyzed hemidiaphragm. These crossed contractions appeared only when all the motor fibers in the active phrenic were blocked but did not subside until after complete recovery

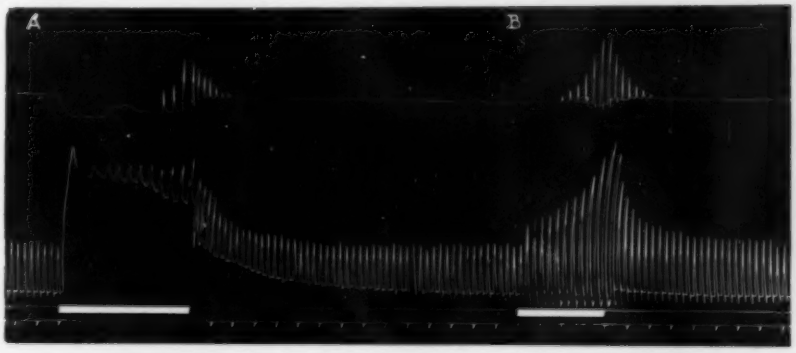

FIG. 1. Rabbit; dial. Left spinal semisection at C2. Electrodes on intact right phrenic below C6; C7 cut centrally to the phrenic. Records from Head's slips; upper: left; lower: right. In this and the succeeding figures the time signal registers 5-second intervals.

A. Faradic stimulation of the right phrenic. Coil distance: 12 cm. and 60° angle.

B. Tracheal cannula occluded for the same time.

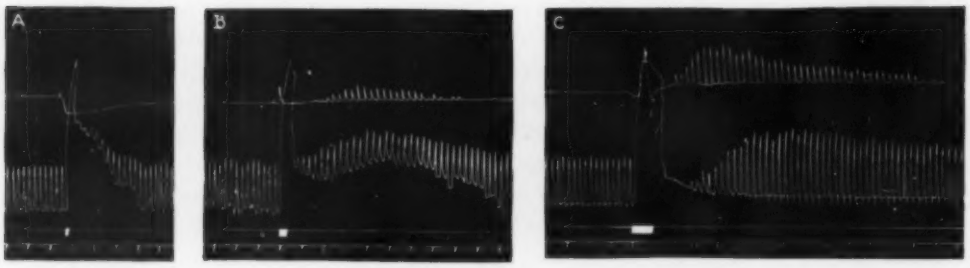

FIG. 2. Same preparation and records as in Fig. 1. Faradic shocks delivered to the right phrenic; coil distance 8 cm. A: 1 sec. B: 2 secs. C: 5 secs.

of the blocked phrenic. In the phase of subsidence, therefore, both hemidiaphragms, direct and crossed, contracted simultaneously for some time.

The purpose of the present observations was to study the influence of various intensities and durations of the reversible blocks on the delay, magnitude and time-course of the crossed effects. For this reason alternating and direct current were used since they can be accurately gauged as blocking agents, and were preferable to ether. In general it may be stated that as the blocking currents are intensified or applied for longer periods, thus increasing the block, the crossed effects come earlier and are bigger and more prolonged. If very weak A.C. or D.C. currents are used, which do not lead to blocking of the motor nerve fibers even when applied for long periods (up to 1 min.), no crossed contractions appear as a rule. When they do occur they are delayed and small, and are probably due to relative asphyxia of the animal (see next section) because of the prolonged tetanic contraction of the active hemidiaphragm.

Stronger currents, capable of producing complete block, if applied for a few seconds, result in crossed contractions. The longer the duration of the block,

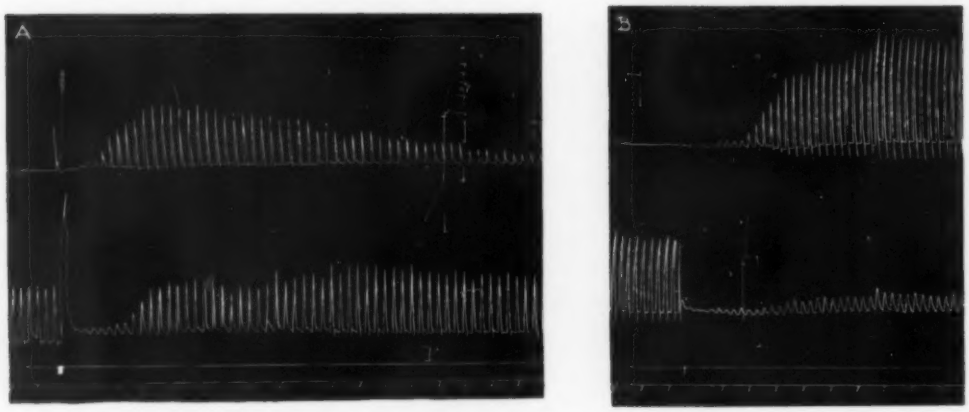

FIG. 3. Same preparation and records as in Figs. 1 and 2.
A. Faradic shocks delivered to the right phrenic for 1 sec.; coil distance: 7 cm.
B. At signal section of the right phrenic.

the more prolonged the crossed effects. Blocks of similar duration can be produced by currents of different intensity by adjusting the periods of application. Thus, a brief strong current may result in a complete block of the same duration as that produced by a weaker current applied for a longer period. In such cases there is a tendency for the stronger current to elicit more marked crossed effects—*i.e.*, stronger and more prolonged—than those brought out by the weaker current. Figs. 1, 2 and 3 illustrate some of the points mentioned. In Fig. 1 it is shown that the small delayed crossed contractions elicited by

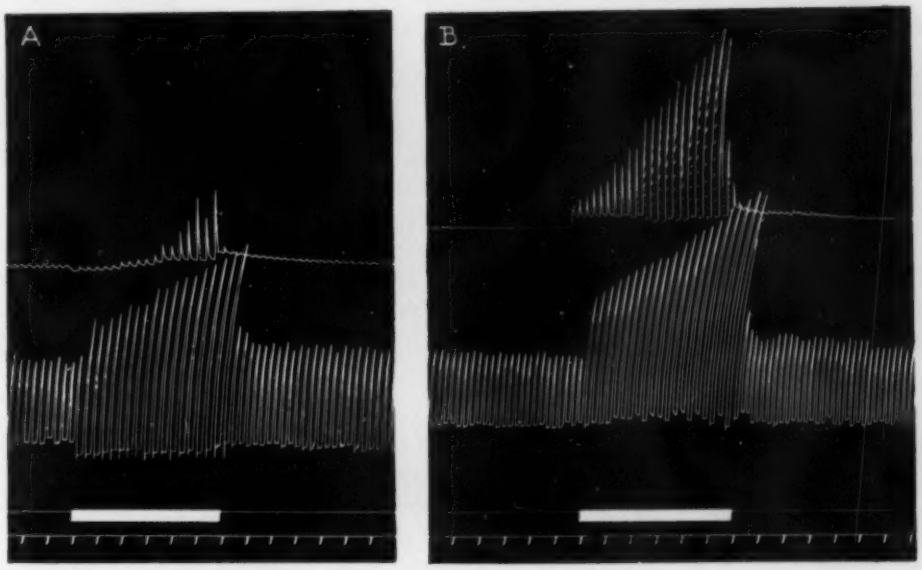

FIG. 4. Effects of asphyxia before and after reversible crossing. Cat; dial. Left spinal semisection at C2. Right C7 cut. Head's slips; upper record left, and lower record right hemidiaphragm. At signal, tracheal cannula occluded.

A. Before any reversible crossing.

B. After three reversible crossings from the application of A.C. to the right phrenic below C6.

prolonged non-blocking stimulation of the active phrenic closely resemble the contractions evoked by a similar period of asphyxia. In Fig. 2 the increasing effect of increasing duration of the blocking A.C. is demonstrated. In Fig. 3 the similarity in the onset of the crossed contraction elicited by a strong block and by cutting the phrenic is emphasized.

Respiratory reflexes and asphyxia. The purpose of these observations was to compare the effects of increased respiratory discharges on the hemidiaphragm paralyzed by a high spinal semisection, before and after the application of a reversible block to the active phrenic. The experimental procedure consisted in making a left spinal semisection at C2 and applying stimulating electrodes on several afferent nerves and sometimes also on the active right phrenic. The results of stimulating the afferent nerves and of asphyxia were

then observed and recorded from the two hemidiaphragms. After these preliminary records were obtained, one or more reversible ether or electrical (A.C. or D.C.) blocks were applied to the right phrenic. These blocks resulted in a transient appearance of respiratory contractions of the left, previously paralyzed hemidiaphragm. The afferent nerves were then again stimulated and asphyxia produced, as before the reversible crossings.

Rosenblueth and Ortiz (1936) reported that asphyxia did not lead to any crossed contractions unless it was applied after a reversible crossing had been obtained by a transient block of the active phrenic. In the present observations, in some animals (rabbits and cats) a crossing was observed during

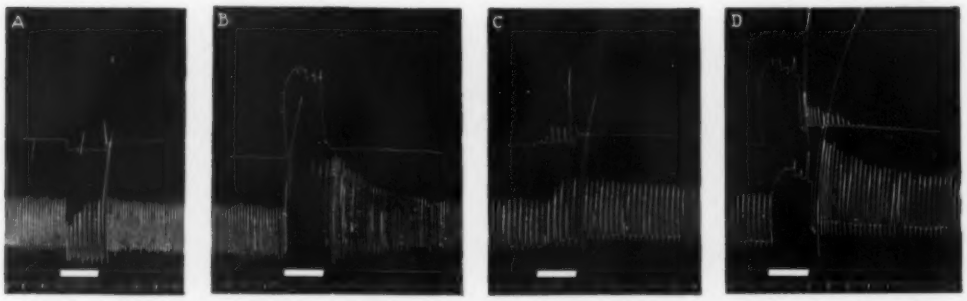

FIG. 5. Appearance of crossed reflex contractions after reversible crossing. Rabbit; dial. Left spinal semisection at C2. Right C7 cut. Head's slips; upper record: left, and lower: right. A and B, before any crossing had occurred. C and D, after two reversible crossings from the application of A.C. to the right phrenic below C6. A and C: afferent stimulation of the right median nerve (coil distance 8 cm.). B and D: afferent stimulation of the left vagus (coil distance 8 cm.).

asphyxia in the preliminary control records. Such crossing did not occur, however, until the asphyxia was pronounced, and subsided promptly upon cessation of the asphyxiating procedure (Fig. 4A). Production of a similar degree of asphyxia after one or more reversible crossings elicited prompt, vigorous crossed contractions, which did not cease immediately when the animal was allowed to breathe freely (Fig. 4B). The results of afferent stimulation in rabbits were similar to those of asphyxia. Crossed contractions occurred in some animals before any reversible blocks had been applied to the active phrenic. Such reflex crossed contractions were, however, as a rule delayed and weak, and subsided promptly after cessation of the stimuli. After one or more reversible crossings, on the other hand, the reflex effects were more prompt, vigorous and enduring than before. Fig. 5 illustrates a typical instance.

Effects of cutting the vagi. Section of the vagi in normal rabbits results in respiratory changes similar to those found in cats and dogs—*i.e.*, the respiration becomes slower and deeper. In rabbits with a high spinal semisection in which the vagi are cut before any crossed diaphragmatic contractions have been produced by blocking or cutting the active phrenic, the results of cutting the vagi are the same. In the rabbits in which the vagi were cut after the active phrenic had been severed, or only reversibly blocked, the change of the

respiratory frequency consisted usually in an acceleration (Fig. 6). Similarly, in the operated rabbits reported in section A, cutting the vagi produced a respiratory acceleration. These results are summarized in Table 3. In the cats, whether the vagi were cut before or after crossing, the effect was usually a slowing of the respiration.

Another consequence of severing the vagi is the following. In animals, cats or rabbits, in which no reversible crossed effects had been elicited, such a section did not result in crossed contractions. But if one or more reversible blocks, with the corresponding transient crossings, had been applied, then sec-

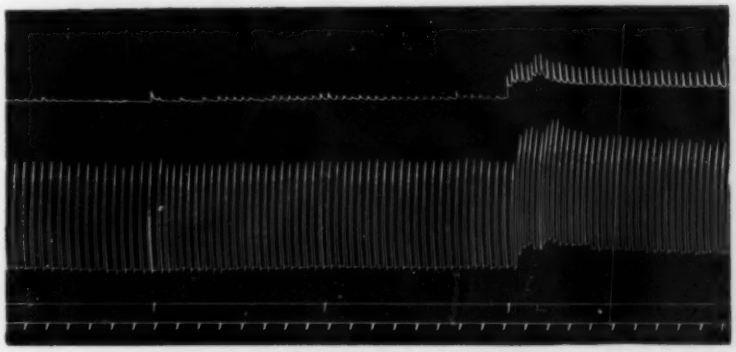

FIG. 6. Rabbit; dial. Left spinal semisection at C2. Head's slips; upper: left; lower: right. Before this record was taken 4 reversible crossings had been produced by application of D.C. to the right phrenic. At signals: first, section of right vagus; next, section of right cervical sympathetic; last, section of left vagus.

tion of the vagi frequently led to the immediate appearance of crossed contractions, which subsided slowly. Fig. 6 illustrates a typical instance. It may be recalled that in the operated animals section of the vagi led also in several cases to the appearance of crossed contractions (Tables 1 and 2).

Changes of rate during crossing. In the *rabbits*, whether the crossing was transient, by applying a reversible block to the active phrenic, or permanent, by cutting the nerve, the respiratory rate was usually slower during the period of crossed contractions than before the crossing. This slowing was observed in various experimental conditions summarized in Table 4. Figure 7 illustrates typical instances. In the *cats* the changes of rate during crossing were less marked than in the rabbits. They consisted usually in a slowing followed by recovery of the normal rate, although the crossed contractions persisted.

DISCUSSION

Rosenblueth and Ortiz (1936) reported that in some cats a high spinal semisection did not lead to an ipsilateral respiratory hemiplegia. In the present experiments a respiratory hemiplegia was absent only when the spinal semisection was incomplete. In the rabbit, as Porter (1895) pointed out, all the nerve fibers descending from the respiratory center to the spinal motoneu-

rons travel superficially in the external region of the lateral columns. Even a small section of the cord in this region, not reaching the nerve fibers in the neighborhood of the midline, will, therefore, usually result in an ipsilateral respiratory paralysis. In the cat, on the other hand, there probably are some descending respiratory fibers placed medially, besides the lateral tract analogous to that in the rabbit. For this reason an incomplete semisection will fail to paralyze entirely the corresponding respiratory muscles. Once this condition was recognized the spinal sections in cats were made to overlap the midline and invariably resulted in the desired hemiplegia. Indeed, cats may be more satisfactory than rabbits for the study of the phenomenon, in as much as crossed contractions upon blocking or cutting the active phrenic have occurred

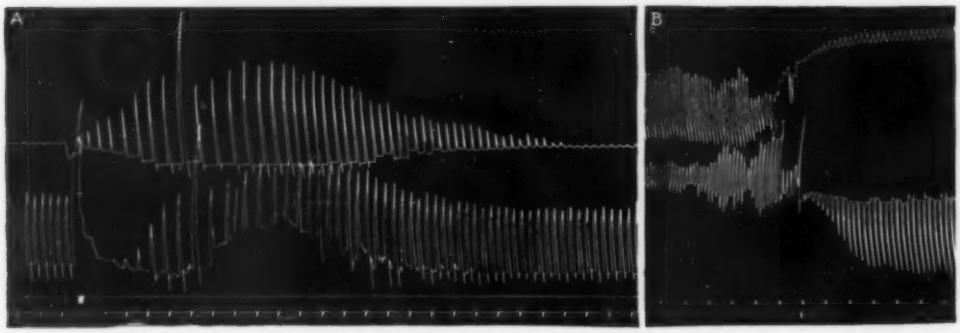

FIG. 7. Slowing of the respiration during crossed contractions.

A. Rabbit; dial. Left spinal semisection at C2 and complete transection at C7. Head's slips; upper: left; lower: right. At signal A.C. (coil distance 8 cm.) applied for 1, sec. to right phrenic below C6.

B. Rabbit; dial. Left spinal semisection at C2. Vagi, cervical sympathetics and depressors cut. Records from the diaphragmatic domes; upper: right, lower: left. At signal, right phrenic cut.

in all the cats tested, whereas occasionally the crossed contractions have entirely failed to appear in some rabbits. Rosenblueth and Ortiz (1936) reported 4 rabbits in which no crossing took place. These 4 animals had had a bilateral section of the vagi, cervical sympathetics and depressors, before the active phrenic was blocked or cut. It was thought that the previous operations were responsible for the absence of the crossed contractions.

This inference was invalidated in the present series of rabbits by 4 animals in which a prompt typical crossing occurred upon cutting the active phrenic after cranial nerves IX, X, XI and XII and the cervical sympathetic trunks had been cut. Other instances of lack of crossing in rabbits were again encountered here, and no correlation could be established with the experimental procedures, the strains of rabbits used, the anesthetic employed or the depth of anesthesia. Unless the animals are grossly over-anesthetized, crossing may occur under ether, dial, dial with additional urethane, urethane alone or chloralose. In the total number of normal rabbits (*i.e.*, unoperated previously) used thus far in this Laboratory for the study of the phenomenon, there have

been 10 instances of negative results—*i.e.*, no crossing on cutting the active phrenic, or by any other procedure—as opposed to 50 positive instances. These figures are of importance in judging the results obtained in the operated animals.

It is significant that 3 out of the 9 cats and 6 out of the 19 rabbits in which a phrenic had been previously cut did not present an immediate crossing upon performing a contralateral high spinal semisection (Tables 1 and 2). That the absence of crossing in such conditions is probably correlated with the functional regrowth of the cut nerves into the structures to which they had been anastomosed is indicated by the fact that with the exception of only 2 animals an immediate crossing occurred whenever there was no evidence of regrowth. Indeed, it is possible that in the exceptional animals a slight regrowth was present but not detected. If the appearance of the crossed contractions were due to either relative asphyxia or to quantitative changes in the number and distribution of afferent impulses set up by the respiratory movements, an immediate crossing would have taken place in all the operated animals upon performing the high spinal semisection, regardless of whether the cut phrenics had regrown into other structures or whether such regrowth had not occurred. Since this was not the case, however, the evidence from the operated animals supports the conclusion previously reached (Rosenblueth and Ortiz, 1936) that the crossing is not primarily due to either asphyxia or changes in afferent bombardment of the centers.

The evidence obtained by electrical stimulation of the respiratory center or the respiratory tract supports this conclusion more directly. The number of nerve impulses delivered to the phrenic motoneurons was probably constant, since the stimulus was not varied. Complete paralysis of the respiratory muscles except during stimulation and uniform artificial respiration eliminated any significant changes in afferent bombardment. Yet crossed contractions only appeared after the phrenic on the direct side was cut. The inference again emerges that the crossing is due to section of the motor axons in the phrenic. Such a section is followed by changes in the phrenic motoneurons or related internuncials in the spinal cord, so that the descending respiratory impulses then become able to activate liminally the contralateral phrenic motoneurons.

The experiments on the effects of A.C. or D.C. blocks of different intensities and durations (Figs. 1, 2 and 3) are in agreement with the previous conclusions. When the current applied to the active phrenic is not sufficiently strong to block all the motor fibers, no crossing occurs. This is in keeping with the similar facts reported by Rosenblueth and Ortiz (1936) when ether blocks were employed, or when the phrenic was cut in stages by sectioning the cervical nerves progressively. If asphyxia or changes in afferent nerve impulses played a major part in the phenomenon, the crossing should take place even when only some of the motor fibers are inactivated and should be approximately proportional to the number of fibers blocked. Such is not the case.

The crossed effects are, on the other hand, a function of the magnitude

(intensity and duration) of the block produced, since they are more prompt, greater and more prolonged, the deeper and longer the block of all the motor fibers (Fig. 2). Notwithstanding this proportionality the records reveal an independence of the time course of the block on the direct side and the respiratory contractions on the crossed side. Depending upon the intensity and duration of the blocking currents applied, the subsidence of the crossed effects may be rapid and begin while only a few of the blocked motor fibers have recovered, or it may be slow and begin after all the motor fibers on the direct side have recovered from the block. It may therefore be concluded that the central effects of the block are a function of its magnitude, but are independent of the changes in the respiratory movements which the block elicits.

The observations (Figs. 4 and 5) also support the conclusion that once the crossed path has been opened by a reversible block subsequent crossings are more readily obtained and more pronounced (Rosenblueth and Ortiz, 1936). When the effects of the reversible block have subsided, although the original condition seems reëstablished, the centers have really different properties in this respect, at least as long as the experiment lasts. This central change takes place probably at the spinal cord, since the discharges of the respiratory center during asphyxia or the reflexes, as judged by the contractions of the direct side, are no greater after the block than before its application.

In dogs, section of the vagi leads usually to the permanent appearance of crossed discharges (Rosenblueth and Ortiz, 1936). In normal—*i.e.*, not previously crossed—rabbits or cats, section of the vagi has never been observed to result in crossed contractions. On the other hand, the influence of the vagi on the crossed phenomenon is apparent in the animals in which the section is made after a crossing has taken place (Fig. 6; Tables 1 and 2). The difference between the dogs and cats or rabbits may therefore be only quantitative in this regard. With the data available, the problems of the mechanism, site and nature of the central changes produced by section or blocking of the phrenic are open only to speculation. The present observations offer, however, some clues worthy of consideration. As shown above (pp. 510, 514) the experiments suggest that some of the changes take place in the spinal cord—phrenic motoneurons or possible internuncial neurons—as opposed to the medullary cells of the respiratory center. Such evidence might be explained by postulating changes in only the cut or blocked neurons.

The data in Figs. 6 and 7 (See Tables 3 and 4), suggest on the other hand, that the effects of section or block transcend the neurons directly affected. Changes of rate which involve not only the diaphragm, but also all other respiratory muscles, are to be attributed to modifications taking place in the respiratory center.

It thus appears likely that the local changes in motor fibers to which electric currents are applied for a brief period have a widespread influence on the properties of central neuron systems. The propagation occurs by some mechanism different from that by which nerve impulses are conveyed. The changes are probably not unineuronal, but extend beyond the synaptic confines.

Table 3

Changes in respiratory rate upon cutting the vagi in rabbits. The figures indicate the number of animals in which the corresponding phenomenon was observed.

	Acceleration	No change	Slowing
Normal rabbits			
Before any crossing	3	5	17
After one or more reversible crossings	7	1	1
After cutting the active (direct) phrenic	2	0	0
Operated rabbits	14	3	0

Table 4

Changes in respiratory rate during crossing in rabbits. The figures indicate the number of animals in which the corresponding phenomenon was observed.

	Acceleration	No change	Slowing
Phrenic cut. Vagi intact	0	0	5
Phrenic cut. Vagi cut	2	1	7
Ether blocks. Vagi intact.	0	3	5
Ether blocks. Vagi cut.	2	1	3
A.C. blocks. Vagi intact.	0	0	2
A.C. blocks. Vagi cut.	0	1	2

Summary

The appearance of crossed diaphragmatic contractions—*i.e.*, ipsilateral to a spinal semisection at C2 or C3—was studied in rabbits and cats in the following experimental conditions: (i) animals in which the phrenic nerve contralateral to the spinal semisection had been cut and anastomosed either to the cervical sympathetic or the denervated sternomastoid muscle 1 to 25 weeks previously (Tables 1 and 2); (ii) animals in which the respiratory center or the respiratory tract above C3 was stimulated electrically; (iii) animals in which the active phrenic on the side contralateral to the spinal semisection was blocked reversibly by alternating or direct currents of various intensities and durations (Figs. 1, 2 and 3); (iv) during activation of the respiratory center either reflexly or by asphyxia, before and after application of reversible blocks to the active phrenic (Figs. 4 and 5).

The effects of cutting the vagi before or after reversible diaphragmatic crossings are described (Table 3, Fig. 6). The changes of respiratory rate during crossings are reported (Table 4, Fig. 7). In the discussion it is shown that the following conclusions are confirmed: (i) crossed contractions occur directly as a result of cutting or blocking the motor fibers, not as an indirect effect from relative asphyxia or from changes in the afferent impulses set up by respiratory movements; (ii) the central changes are mediated by some process which does not require the conduction of nerve impulses; (iii) once the crossed path has been opened—*i.e.*, after a reversible block—subsequent crossings are more

readily obtained. The facts reported also suggest that some of the central changes responsible for the crossing occur at the spinal cord (pp. 510, 514). Other data (p. 513) show that in addition to these lower spinal changes there are probably also modifications in the respiratory center in the medulla, caused by the block or cut of the phrenic which leads to crossing.

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A FOURIER TRANSFORM OF THE ELECTROENCEPHALOGRAM*

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THE electroencephalogram as usually recorded shows a confusion of wave forms and a mixture of frequencies which are impossible of accurate visual analysis. With experience one can learn to detect certain gross features which have significant clinical and physiological correlates, but in this there is more art than science. Certain crude indices which have been devised as a basis for comparison are open to theoretical criticism. They are not arrived at objectively, and do not afford a consistent expression for the data. The electroencephalogram, which is an amplitude *vs.* time function, can be expressed as a continuous plot of amplitude *vs.* frequency; that is, as a spectrum. The mathematical tool for making such a transposition is the Fourier Transform. The validity of expressing data of the type found in the electroencephalogram in terms of its Fourier Transform is generally recognized.[1,2] The only question that can be reasonably argued is whether such an expression is advantageous. We believe that it is, and have applied the Fourier Transform to a large number of electroencephalograms. The theoretical and practical advantages of this expression will be set forth below.

Not the least of its advantages is the simplicity with which it can be obtained by the mechanical-electrical integrator which one of us (A.M.G.) has designed. The technique is as follows: A representative oscillogram is taken as a shadowgraph on 35 mm. film, and later made into a continuous function by splicing the film to form an endless belt. The belt is revolved between a transverse slit of light and a photo-electric cell which reproduces the original electroencephalogram (Fig. 1). The resulting signal is passed through an extremely sharp variable electric wave filter. The speed of the belt and the speed of the frequency scanning mechanism is so arranged that the electroencephalogram to be analyzed can be treated as a repetitive function in this system. After being rectified the output of the filter is connected to a galvanometer which automatically records the amplitude of each differential frequency component on sensitized coördinate paper.

No objective method of analyzing the intricate wave forms of the electroencephalogram has previously been devised. The advantage of such a method in practice is that it is independent of the several intricate and arbitrary terminologies which have been devised for compiling results of studies on the electrical activity of the brain. It affords a relatively complete yet comprehensive expression for the data in terms of itself alone. It provides a common, rigorous, and mathematical expression for all types of record. Furthermore it ends the tedious work of measuring frequency by hand, and of estimating for

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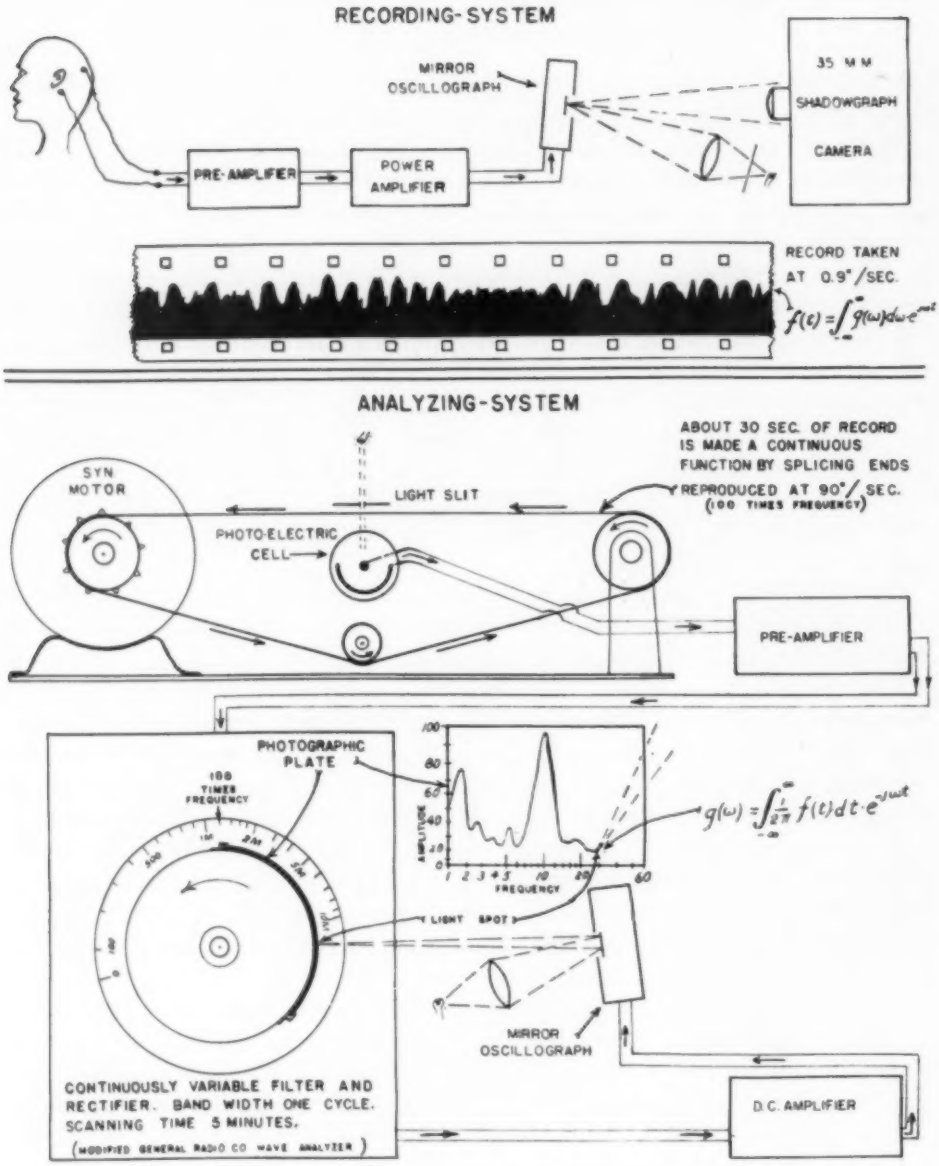
RECORDING-SYSTEM
MIRROR OSCILLOGRAPH
35 M M SHADOWGRAPH CAMERA
PRE-AMPLIFIER
POWER AMPLIFIER
RECORD TAKEN AT 0.9"/SEC.
$f(t)=\int_{-\infty}^{\infty} g(\omega)d\omega\, e^{j\omega t}$
ANALYZING-SYSTEM
ABOUT 30 SEC. OF RECORD IS MADE A CONTINUOUS FUNCTION BY SPLICING ENDS
REPRODUCED AT 90°/SEC. (100 TIMES FREQUENCY)
SYN MOTOR
LIGHT SLIT
PHOTO-ELECTRIC CELL
PRE-AMPLIFIER
PHOTOGRAPHIC PLATE
100 TIMES FREQUENCY
AMPLITUDE
FREQUENCY
$g(\omega)=\int_{-\infty}^{\infty}\frac{1}{2\pi} f(t)dt\cdot e^{-j\omega t}$
LIGHT SPOT
MIRROR OSCILLOGRAPH
CONTINUOUSLY VARIABLE FILTER AND RECTIFIER. BAND WIDTH ONE CYCLE. SCANNING TIME 5 MINUTES.
(MODIFIED GENERAL RADIO CO WAVE ANALYZER)
D.C. AMPLIFIER

FIG. 1

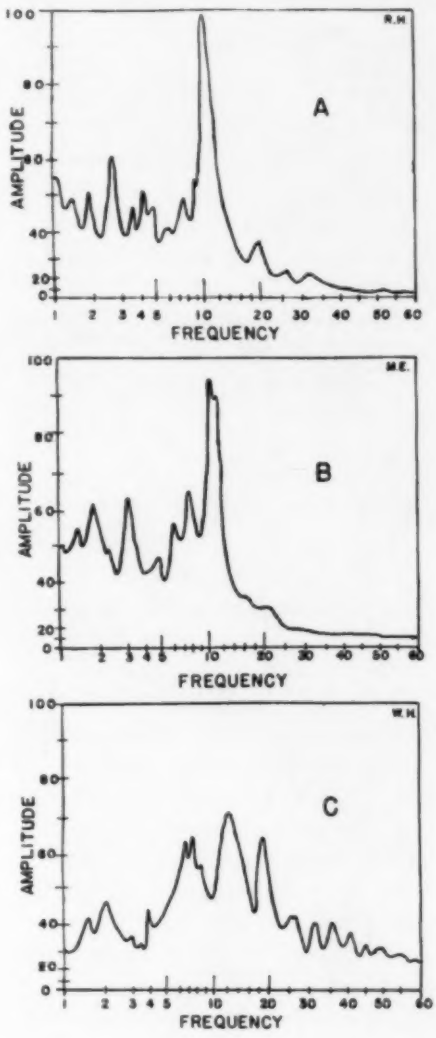

FIG. 2
3 NORMALS

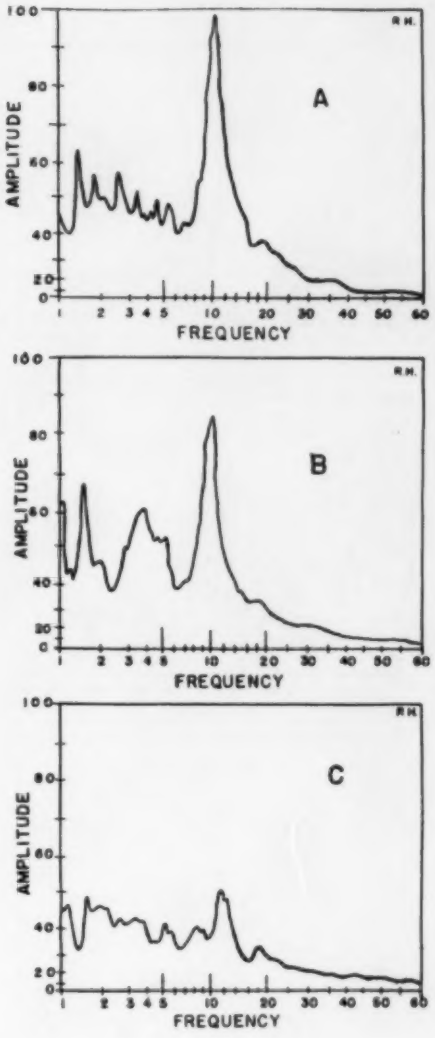

FIG. 3
A- NORMAL, EYES CLOSED
B- EYES OPEN, INACTIVE
C- EYES OPEN, READING

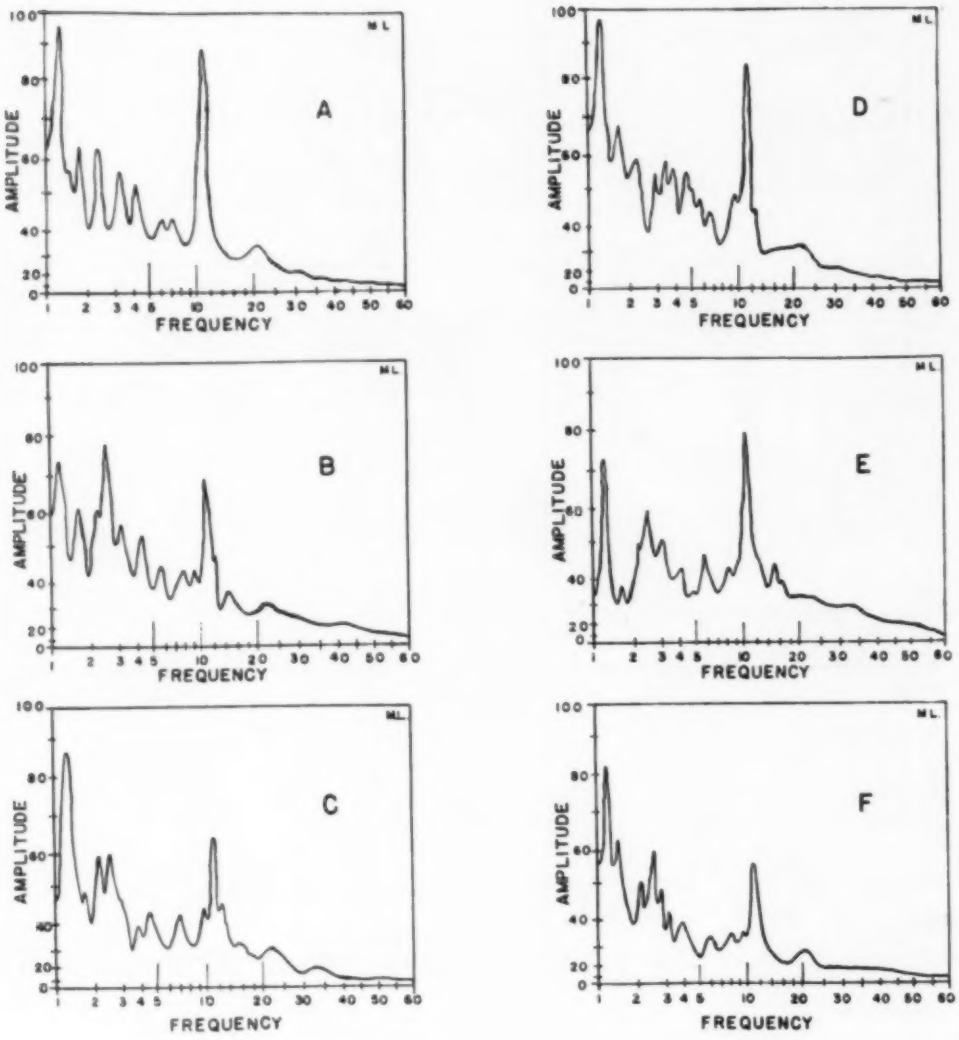

FIG. 4

ANALYSES OF RECORDS OF A NORMAL TAKEN AT 10 MINUTE INTERVALS

each component the percentage of time present, both of which procedures are as exhausting as they are inadequate and inaccurate.

The Fourier Transform is not proposed as a substitute for the customary oscillographic recording of the electroencephalogram, but rather as a supplement and a compact expression for such a record. The unanalyzed record is still indispensable for detecting short bursts of particular wave forms, phase relations, and "build-ups," all of which have been shown to be significant. These tend to be lost in the analyzed record. Nevertheless, the time element can be supplied in the form of consecutive analyses made at separate or continuous intervals of time.

Analyses have thus far been made of more than 300 records. These include a control group of 111 normals, 104 schizophrenics, and 84 epileptics. In many of the subjects observations were repeated at different intervals of time. In all cases records were taken from frontal, occipital, parietal and temporal lobes. Comparisons and data for these cases is being worked up and will be published in the near future. Analyses of the normal electroencephalograms made with leads on the left occipital area and on the ear reveal that energy is scattered over all frequencies from below 1 to approximately 60 cycles per sec., a range in which we are particularly interested. But more energy is found at cer-

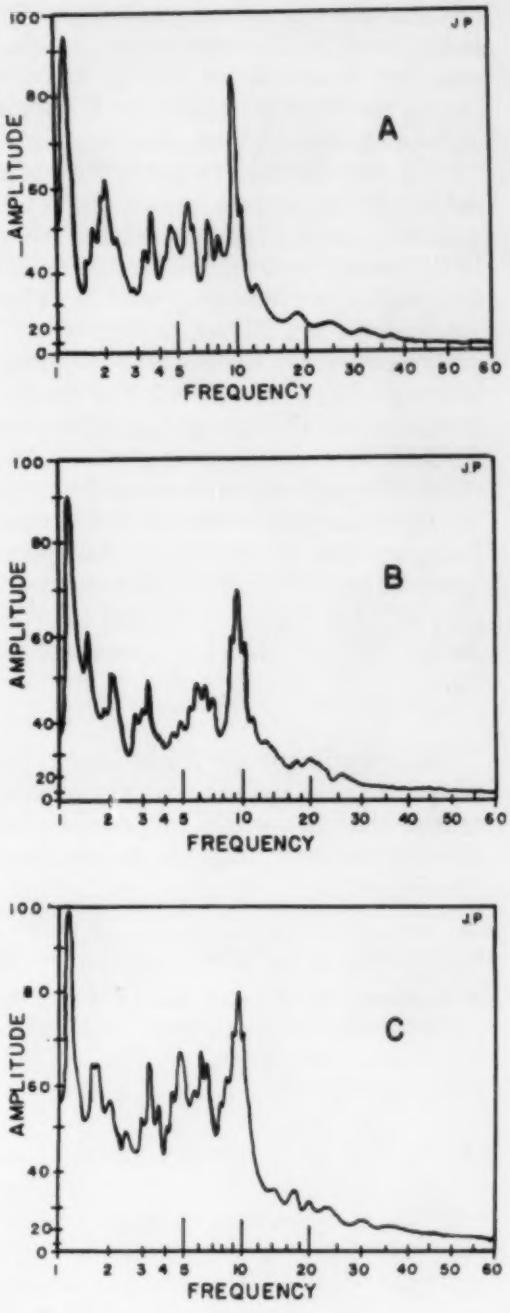

FIG. 5

ANALYSES OF A NORMAL'S RECORDS AT TWO DAY INTERVALS

tain group frequencies than at others. The most constant peaks are to be found in 1–12 and 18–22 cycles per sec. bands. Fourier Transforms from various normal records are shown in Fig. 2. Inspection of such continuous spectrums should convince one of the inadvisability of referring to certain potentials as alpha, beta, delta waves, etc.

Fig. 3 shows the changes in the analyzed electroencephalogram of a normal subject sitting at rest (A) produced by opening the eyes (B) and by reading (C). Inspection of these analyses will reveal data which are entirely hidden in the unanalyzed record, for example, the exact position of the 20 cycles per sec. peak. Such data may well be as important as observations which can be made on the unanalyzed record.

Transforms of electroencephalograms taken at ten-minute intervals during an hour (Fig. 4) and at two-day intervals (Fig. 5) indicate that although the electrical activity of the cortex may remain fairly constant, it does change. To determine the exact range through which it changes and the significance of these changes is more important than its "constancy." The center of area of the spectrum with respect to the frequency axis gives a numerical value which indicates how the energy of the spectrum changes from one group of frequencies to another from time to time and with administration of drugs, oxygen, etc. This figure as applied to several series of transforms appears to be useful. The true center of area which includes amplitude may also prove useful.

Summary

After having made transforms of 300 electroencephalograms, we are convinced that the system not only expresses data in a manner more useful and concise than is possible by present methods, but that in many cases it indicates important changes in the electroencephalogram which would otherwise remain hidden.

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THE INFLUENCE OF CYANIDE ON BRAIN POTENTIALS IN MAN

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PORTER, Blair and Bohmfalk (1938) report that NaCN has a facilitating effect on motoneurons in the spinal cord of the cat. It occurred to us that cyanide might be useful for studying the behavior of cells in the cerebral cortex of man. NaCN is a strong respiratory stimulant in sub-convulsive doses (Loevenhart, *et al.*, 1918), the carotid sinus being its site of primary action (Heymans, Bouckaert and Doutrebande, 1931). Thus cyanide may be used safely in man, with the special advantage that one can readily ascertain when it reaches the carotid sinus, and, consequently, when it can be expected to reach the brain.

METHODS

Schizophrenic patients were used, since they were routinely receiving NaCN for arm-to-carotid sinus circulation time determinations by the method of Robb and Weiss (1933) and Freeman (1934). Normal individuals respond to NaCN in the same fashion as the patients. A group of 19 patients were given intravenous injections of 0.7 cc. of 2 per cent solution of NaCN (equivalent to 14 milligrams) via the antecubital vein near the elbow. In addition, the effect of cyanide on the electroencephalograms of a narcoleptic and a stuporous catatonic were observed.

Brain potentials were recorded on paper tape from electrodes placed on the scalp over various cortical regions, suitable amplifiers being used. A more detailed description of the recording technique may be found elsewhere (Rubin, 1938).

RESULTS

NaCN in the doses used here produced a series of deep gasps which occurred from 15 to 20 secs. after the injection and lasted for 10 to 20 secs. The following brain potential responses most frequently took place immediately after the respiratory response ceased or, in some cases, not until as much as 30 secs. later. The time for full return to the pre-NaCN level of cortical activity was usually about 2 mins. There seemed to be no relation between the severity or duration of the respiratory response induced by cyanide and the resulting brain potential changes.

In 12 patients out of 19 an increase in amplitude, regularity and amount of alpha (10/sec.) activity was observed, followed in a few instances by a decrease. In addition, higher frequencies became more predominant and slow irregular rhythms tended to disappear. Frequency remained unaltered. An initial, slight depression of alpha activity was observed in three subjects, followed in one case by an increase above the pre-NaCN level. The other four patients showed no change in their electroencephalograms.

It is well known that the first effect of cyanide is an excitatory one, if the concentration is not too great; in still higher concentrations it is a depressant

agent. It is reasonable to suppose that in the three subjects who showed a depression of cortical activity, the concentration of cyanide was considerably greater than that which would have resulted in excitation for those individuals. Unfortunately, we did not try different dosages of NaCN, but used the same amount for all subjects. It is possible that the cyanide dosage was below threshold for the four individuals whose brain potentials remained unaltered.

The general response to NaCN seems to be an increase of activity in cortical cells which are capable of producing the alpha rhythm, and greater regularity of the rhythm. The most marked effects were obtained from the motor region, although the frontal lobes tended to be equally affected. The parietal

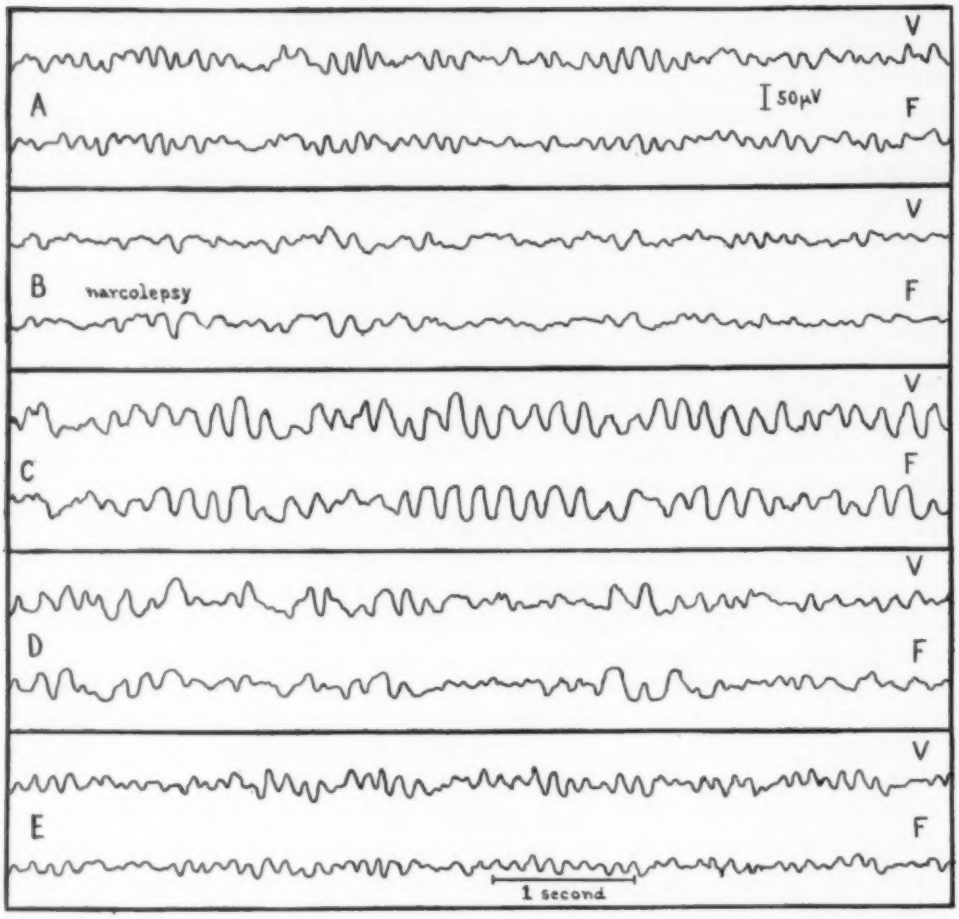

FIG. 1. Simultaneous records from midline electrodes on the vertex (V) and over the mid-frontal (F) region of a narcoleptic. A was taken when the subject first reclined on the bed; B is typical of the narcoleptic state which occurs within a minute or so after the individual lies down; C shows regular 5–6 per sec. waves appearing 20 secs. after stimulation of the carotid sinus by NaCN; D, one-half minute later; E, one minute after D. Amplification constant throughout.

region was least responsive to NaCN, and the occipital alpha rhythm was the most variable, showing no change, an increase or a decrease.

The effect of NaCN on the brain potentials of a narcoleptic individual proved of considerable interest (Fig. 1). In the waking state his alpha rhythm had a frequency of 8 to 9 per sec.; during the narcoleptic state the alpha rhythm was markedly decreased in voltage, only slower frequencies remaining unaltered. After intravenous NaCN, regular 5 to 6 per sec. waves of higher voltage appeared, to be followed later by an irregular potential pattern. Finally, in 2 minutes, the initial pattern was reëstablished.

A more dramatic illustration of the increased tendency towards slower rhythms was observed in a catatonic individual who occasionally went into a stuporous state characterized by failure to perform any voluntary movement. He was fully conscious at all times and had perfect recollection of events which took place during his stuporous periods. In this case stupor was accompanied by a diminution of amplitude of the alpha rhythm and the amount of time it was present (Fig. 2, A and B). One-half a minute after the respiratory response induced by NaCN was over, a rather regular 4 per sec. rhythm suddenly appeared under both the occipital and vertex electrodes. This was followed by irregular bursts of activity with occasional regular periods of slow activity for the next 4 mins. Although the slow rhythm was similar to that described for some epileptics by Gibbs, Gibbs and Lennox (1937), we observed no clinical signs of a seizure associated with it.

Control experiments in which this stuporous individual was given 0.7 cc. of distilled water, instead of NaCN, and also painful stimuli, failed to produce any cortical response. Several days later when he came out of stupor spontaneously cyanide induced changes in his electroencephalogram similar to those described previously for the group of 19 subjects.

Discussion

Several possible explanations of the cortical effect of NaCN are worth considering:

1. *Cardiovascular changes*—The increases in blood pressure and pulse rate following cyanide injection are rather small and could hardly be expected to influence cortical activity. In addition, it is difficult to reconcile a uni-directional cardiovascular change with both slow and fast cortical potentials

2. *pH changes*—Gesell, *et al.* (1930) reported a decrease in blood pH on injection of NaCN into animals. If this caused a decrease in pH of the cerebral cortex we should expect to find a decrease in frequency and amplitude of cortical potentials (Dusser de Barenne, McCulloch and Nims, 1937). This would not account for the observed increase in amplitude of the alpha waves and the absence of alteration of their frequency. It would account for the slow rhythms found in our narcoleptic and stuporous catatonic subjects but not for the increased amplitude of these slow waves.

3. *Hyperventilation*—It is questionable whether sufficient hyperventilation occurred as a result of the respiratory stimulation by the NaCN. Hyperventi-

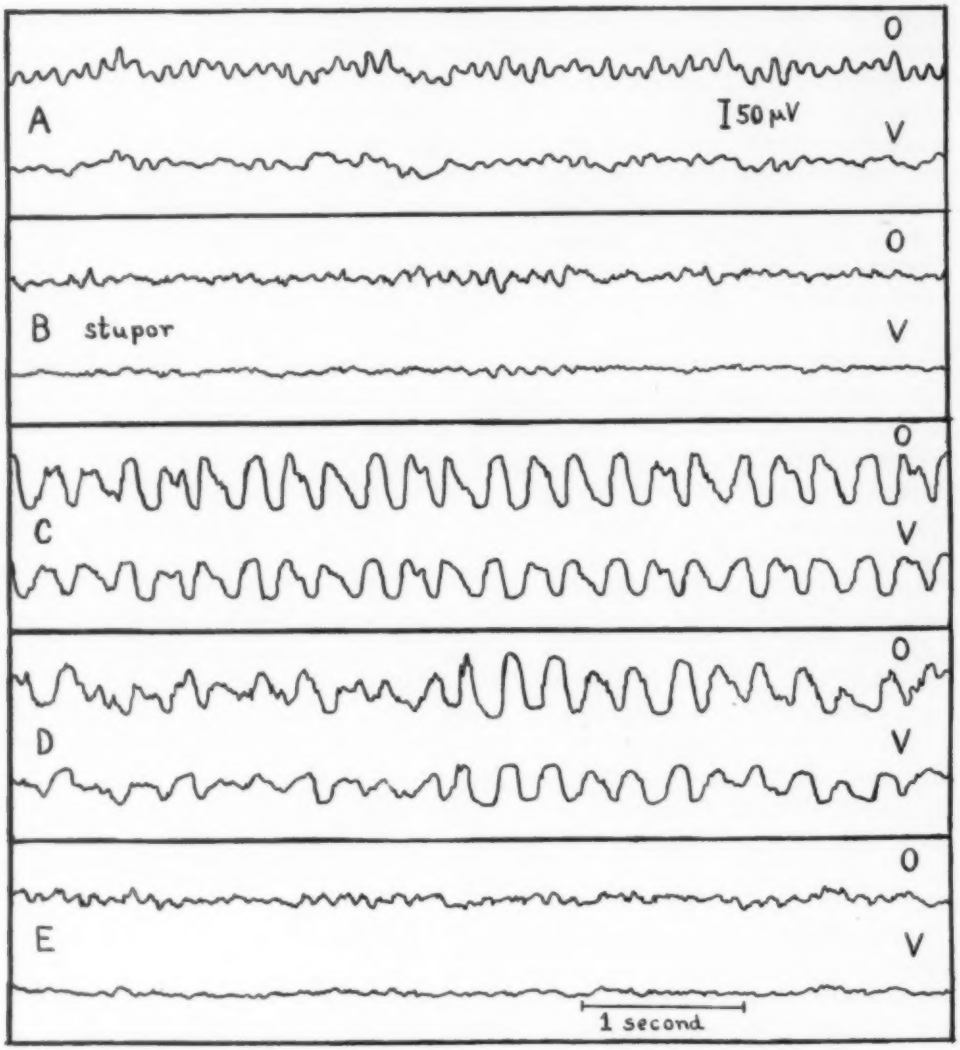

FIG. 2. Simultaneous records from the occiput (O) and the vertex (V), along the midline, from a patient in a catatonic stupor. A, a typical record from this patient when he was not stuporous; B, during stupor and before NaCN was given; C, 30 secs. after the gasping due to intravenous NaCN was over; D, 30 secs. later, illustrating the irregular pattern and an occasional period of regularity; E, at the end of 5 mins. The amplification is the same throughout.

lation, if it were marked enough, would cause an increase in pH of the cortex (Dusser de Barenne, McCulloch and Nims, 1937). However, it is not likely that the pH of the cortex would be increased in the face of a decrease in blood pH. According to Gibbs, Davis and Lennox (1935), the only change in cortical potentials from over-ventilation is the appearance of large 2 to 5 per sec. waves especially when unconsciousness sets in. Our two patients who showed slow

rhythms were not unconscious at any time, and records from the other 19 subjects usually showed less slow activity after NaCN.

It is apparent that the explanation does not lie in the three possibilities just discussed. It is more reasonable to infer that NaCN acts directly on the cortex. As we see it, 15 or 20 secs. after injection of cyanide the carotid sinus is stimulated, setting up afferent impulses to the medulla with subsequent respiratory stimulation. After a lag of another 20 or 30 secs. the cortical response is obtained. The interval between the carotid sinus and the cortical responses must represent the "latent period" of the cortex for the response to cyanide, since the circulation time from carotid sinus to cortex cannot possibly be that long. Porter, Blair and Bohmfalk (1938) give a "latent period" for facilitation in the cat's spinal cord by NaCN of the same order of magnitude, —12 secs., on the average. They concluded that slight asphyxia, due to the NaCN, causes facilitation at the synapses. This would account for the increase in amount and regularity of the cortical alpha rhythm. It might also explain the facilitation of slow rhythms if we assume that cyanide produces synaptic block, rather than facilitation, in a functionally "depressed" cortex. Synaptic block, produced by nicotine, does retard cortical potentials and makes them more regular (Libet and Gerard, 1938). However, the further assumption must be made that "depressed" cortical neurons have a lower threshold to NaCN than normally active neurons, so that concentrations of cyanide which are ordinarily excitatory now become markedly depressant. Such a mechanism would mean that both excitatory and depressant concentrations of cyanide can increase the electrical activity of the cortex and make it more regular.

The importance of the thesis that the pre-existing state of the cortical neurons determines their response at any given time (Blake and Gerard, 1937) is emphasized by our experiments. If the tendency is toward fast activity (*i.e.*, the alpha rhythm) NaCN will enhance it; on the other hand, when the cortex is functionally "depressed" (as in narcolepsy and in catatonic stupor) slow activity, characteristic of subnormal cortical activity, is increased by cyanide.

Summary

Sodium cyanide was injected intravenously into 19 adult male subjects and the resulting changes in potentials from the cerebral cortex were recorded. In general, the alpha rhythm was enhanced, showing an increase in amount of activity, amplitude and regularity. In one narcoleptic and one stuporous catatonic patient, NaCN injection resulted in the appearance of regular, large slow waves. Both effects are interpreted as due to the direct action of NaCN on cortical neurons. The type of response (whether facilitation of fast or of slow rhythms) depends on the pre-existing state of the cortical elements.

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CERTAIN EFFECTS OF PROLONGED STIMULATION OF AFFERENT NERVES ON THE REFLEXES EVOKED

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IT IS a common observation that the strength of the reflex contraction of a striated muscle changes during prolonged stimulation of the afferent nerve, and that if the frequency of stimulation is not too low, the response tends to subside even during stimulation of maximal intensity. A number of workers have investigated the effect of continued stimulation of one afferent nerve on the response of the affected muscles to stimulation of a second afferent. Reflex movements of the hind legs evoked from different skin areas in the strychninized spinal frog were studied by Verworn (1901), and the elicitation of the scratch reflex in the spinal cat and dog by Sherrington (1906). The flexor reflex has been investigated by Lee and Everingham (1909), Forbes (1912), Upland and Michelson (1933), and others; and inhibition of the contralateral extensor by Forbes (1912). The general conclusions of these authors were that subsidence of the response was due to central "fatigue" or "pseudofatigue," and that such "fatigue" of one afferent system did not necessarily affect another afferent system.

If this "fatigue" were of the nature of "exhaustion" at the synapse and if it occurred generally, it would offer a further means for analysis of the spinal and medullary reflex mechanisms. It therefore seemed desirable to extend the observations to other reflexes.

METHODS

Cats were used throughout and were prepared by transection of the spinal cord at T6 or T12, one to eighteen hours before the experiment, or by anaemic or trephine decerebration. In a few cases one of the barbiturate anaesthetics or urethane was given in addition. For observations on the responses from stimulation of the motor cortex the animals were anaesthetized with Dial-Ciba, 0.7 cc. per kg. Reflexes of the hind legs only were studied and particular attention was paid to the ipsilateral flexor (tibialis anticus and gracilis) and the inhibition of the knee jerk. Observations were also made on the ipsi- and contralateral extensors (quadriceps and gastrocnemius-soleus) and the contralateral flexors. Immobilization and fixation were by nerve and tendon section and drills in the bones. Muscular contraction was recorded on a smoked drum by means of levers with heavy rubber bands, or optically by a Sherrington torsion wire myograph. For afferent stimulation electrodes were applied to appropriate peripheral nerves (hamstrings, peroneal, popliteal, femoral), to posterior roots (6th, 7th and 8th lumbar), or to the motor cortex. Several different types of electrodes were tried. The most consistent results were obtained with silver-silver chloride electrodes applied directly to the nerve or through a Ringer's solution-agar bridge. The stimulating current consisted of 60-cycle a.c. through a step-down transformer and potentiometer and of short, diphasic shocks from a photo-electric cell stimulator with a frequency range of 1 to 360 per sec.

Stimulation was always of such strength as to elicit maximal responses. To test the adequacy of the stimulus several devices were used, including increase in the strength of

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the stimulating current, moving the electrodes proximally along the nerve or testing with a second pair of more proximal electrodes. Improvement in the response indicated inadequate stimulus. To control for changes occurring in the muscle the motor nerve was maximally stimulated before and after observations on the reflexes.

The procedure in general was as follows. The muscle was prepared for recording, and stimulating electrodes were applied to two afferent nerves. One afferent was stimulated with a tetanizing current at frequencies of 30 to 360 per sec. continuously for periods of 2 to over 20 min. in different observations. (This will be designated as the *prolonged stimulus* hereafter.) The other afferent was stimulated either by single shocks or by short tetani, 3 to 5 secs., in such a manner and at such intervals as to evoke a constant response. (This will be designated as the *test* stimulus or *test* reflex hereafter). The course of the reflex elicited by the prolonged stimulus and the effect of the prolonged stimulus on the test reflex were noted.

Results

Consistent and reproducible results were obtained over periods of 4 to 5 hours in the spinal preparations. With decerebrate preparations, however, it was often only possible to make 2 or 3 observations, following which the pulse became rapid and feeble, respiration gasping and all reflex activity depressed. This was particularly marked in cases which showed considerable generalized activity during stimulation. In cats under "dial" with intact central nervous system, the response to the initial stimulus was stronger than that to succeeding stimuli unless a period of more than 30 minutes' rest intervened, after which another large response was obtained.

In general two types of behavior of the reflexes resulted from prolonged stimulation: (i) rapid subsidence of the prolonged reflex, with little or no change in the test reflex; (ii) continued reflex activity of both inhibitory and excitatory nature throughout the period of adequate stimulation of the afferent nerve, with modification of the test reflex during and following this period. The former was exemplified best by the flexor reflex, the latter by inhibition of the knee jerk.

Flexor reflex. The results on the flexor reflex coincided with those interpreted as central "fatigue" by previous workers and need not be described in detail. At frequencies of stimulation above 60 per sec. the reflex contraction subsided in 30 secs. to 3 mins. in spinal and decerebrate preparations without anaesthesia, and in 3 to 20 secs. in preparations under dial. Facilitation of the test reflex could be demonstrated for a longer period, usually 1 to 2 mins. After facilitation had also subsided, the test reflex was evoked, in the majority of instances, as in the preliminary control period, and cessation of the prolonged stimulation had no further effect. In a few experiments the test reflex was diminished following the prolonged stimulation. That a considerable proportion of the motor neurons involved in the reflexes were stimulated by both afferents was demonstrated by the phenomenon of occlusion, and in several cases by the fact that each afferent evoked a reflex response which was 60 to 80 per cent of the contraction resulting from stimulation of the whole motor nerve at the same frequency.

This type of independence of the reflex arcs was readily demonstrated for the flexor reflex when either peripheral nerves or posterior roots were used as afferents. The contralateral flexor and the ipsilateral extensor also behaved in

the same way. On rare occasions a similar phenomenon was observed when the test response was elicited by stimulation of the motor cortex, and also rarely in the experiments on other reflexes. In the great majority of the latter experiments, however, quite variable results were obtained, which may be illustrated by the following examples of inhibition of the knee jerk.

Inhibition of the knee jerk. In several experiments on inhibition of the knee jerk the initial response was of the type illustrated in Fig. 1, but in no case was this result obtained after a preparation had been subjected to 2 or 3 periods of stimulation. The characteristic features were as follows. At the beginning of prolonged stimulation the knee jerk was inhibited and the muscle contracted in a more or less smooth tetanus, an ipsilateral extensor reflex. After a few seconds the knee jerk reappeared and was not inhibited again by increasing the intensity of stimulation (at the arrow in Fig. 1). That is, the knee jerk reappeared in the presence of apparent maximal stimulation

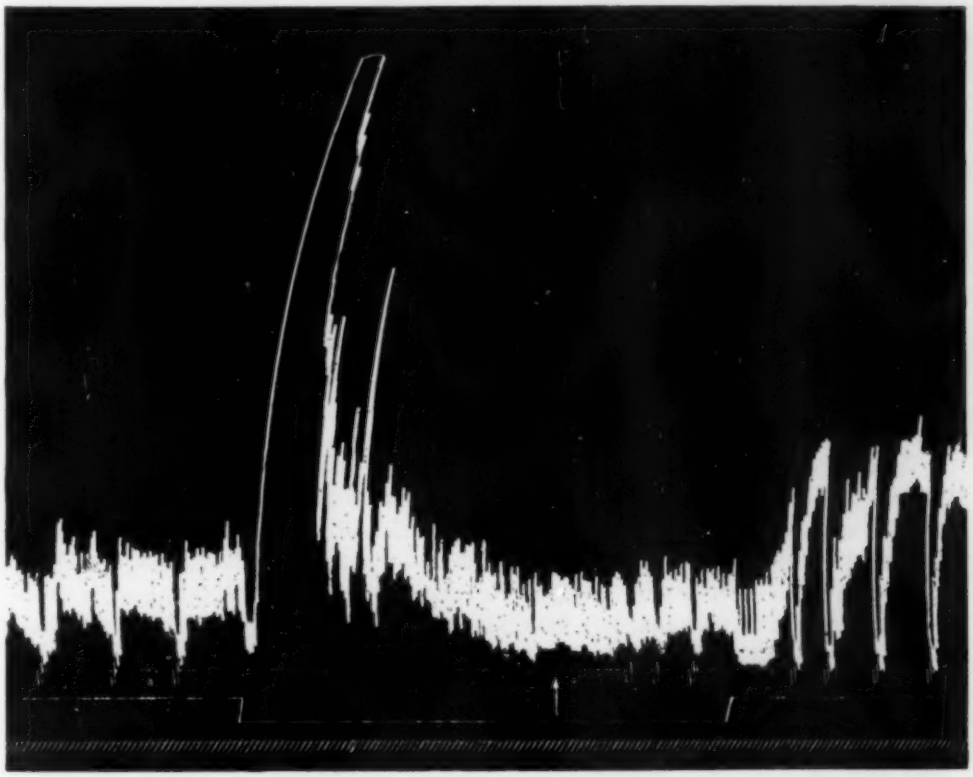

FIG. 1. 3/4/38. Cat, male, 12 hours after transection of the spinal cord at T6. Left quadriceps recording. Knee jerks elicited by electrical hammer twice per second. Upper signal. Single shocks to left peroneal 66σ before next succeeding knee jerk. Photo-electric cell stimulator, 30 volts. Middle signal. Prolonged stimulation of left popliteal, 60 cycle a.c., 5 volts, increased to 10 volts at arrow, ↑. Lower signal. Time in seconds. The flattening of the record at the top of the ipsilateral extensor reflex was due to mechanical interference.

of the afferent nerve. The reappearance of the knee jerk usually occurred when the ipsilateral extensor contraction was at its maximum or had begun to subside. Throughout the period of stimulation there was evidence of continued inhibitory activity (depression of the level of clonus and a short inhibitory after-discharge in the case illustrated). Following a latent period of variable duration on cessation of stimulation a strong rebound contraction occurred which demonstrated the presence of excitatory as well as inhibitory activity during stimulation.

In the example given the test stimuli (single shocks to the peroneal) were equally effective before the prolonged stimulus, after the reappearance of the knee jerk, and during the post-stimulatory rebound contraction, indicating an independence of afferent systems.

In other experiments in which the strength of the ipsilateral extensor contraction was less than that of the knee jerk, it was clear that the latter was inhibited and not occluded during the early phase of the former. Also the effect of the second afferent was to facilitate and not to inhibit the ipsilateral extensor. In both of these respects the ipsilateral extensor and the post-stimulatory rebound contraction appeared to be different phenomena, probably with separate central neural mechanisms.

The common type of response during prolonged inhibition of the knee jerk is illustrated in Fig. 2. This record was selected because it shows the essential features in short compass. Similar results, excepting the two sudden strong contractions during the terminal period of stimulation, were obtained in experiments in which the strength of the stimulating current was gradually increased from 2 to 50 volts over a period of 15 to 20 mins. The presence or absence of clonus or of irregularity of the knee jerk, as in Fig. 2, during the preliminary period did not affect the course of the reaction. At the beginning of prolonged stimulation there was complete inhibition of the knee jerk lasting from 4 or 5 to 50 or 60 secs., and usually a small ipsilateral extensor response. The knee jerk than reappeared, sometimes weak and irregular, sometimes rapidly becoming strong. Increasing the strength of the stimulating current (at the arrow in Fig. 2), or moving the electrodes proximally on the nerve, abolished the knee jerk again for a further period. This could be repeated to the limit of the strengths of current used (50 volts) or to the limit of the length of nerve available. Similar results were obtained with frequencies from 60 to 240 per sec., the duration of the periods of effective inhibition decreasing with increase in frequency. Increasing the intensity of stimulation by large increments did not proportionately prolong the periods of inhibition. The quantitative relationships of these factors were not investigated due to the fact that with repeated stimulation other changes occurred in the preparation as described below. The duration of the excitatory after-discharge varied in different preparations from 1 or 2 to over 40 mins. In general the decerebrate preparations showed greater excitatory after-discharge than the spinal, but the two groups overlapped in this regard and the general condition of the animal appeared to be as important a factor as the level of transection. In

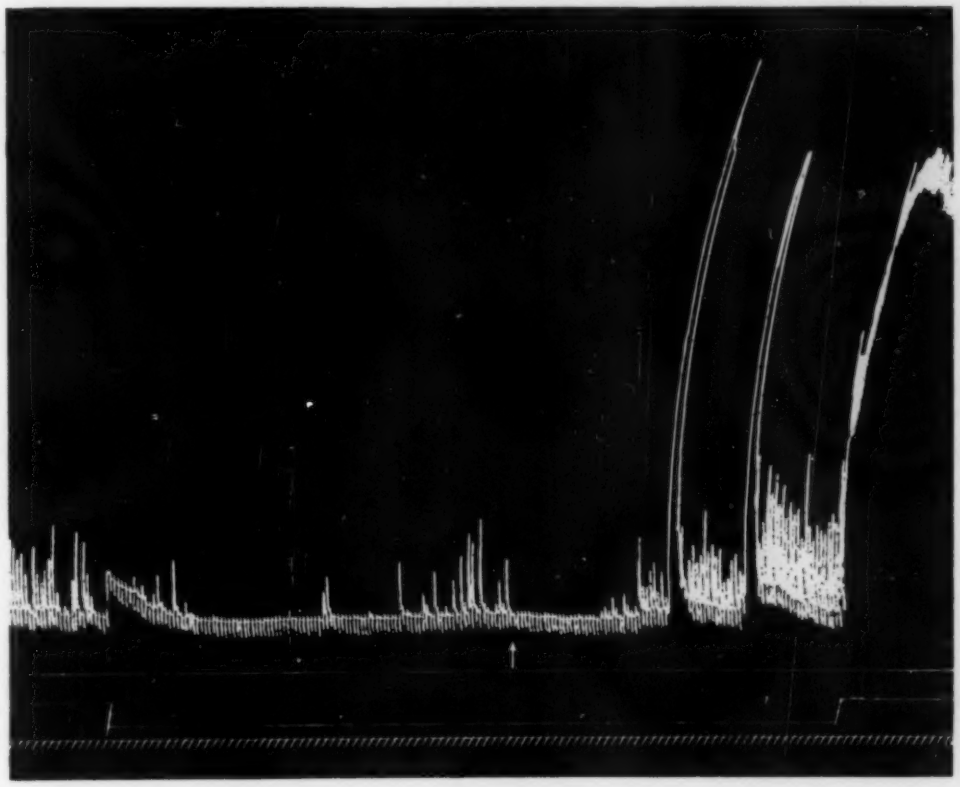

FIG. 2. 2/28/38. Cat, male, 18 hours after transection of spinal cord at T6.
Record and signals as in Fig. 1, except stimulus to popliteal nerve 12 volts, increased to 20 volts at arrow, ↑.

some cases the after-discharge did not appear unless the prolonged stimulation was of at least 2 minutes' duration, but in the majority of instances it appeared after a succession of short (10 to 15 secs.) tetani.

The response of the test reflex in the group of experiments under consideration varied greatly from preparation to preparation. In some there was little change of either the excitatory (ipsilateral extensor) or inhibitory action. In this respect the results indicated a certain independence of the reflex arcs, as was found for the flexor reflex. In other preparations, however, considerable changes of long duration occurred, an example of which is illustrated in Fig. 3. Early in this experiment, Fig. 3A, the ipsilateral extensor response, evoked by a single shock to the peroneal nerve, was small and the after-discharge of inhibition of the knee jerk was profound and long. Figure 3B is a portion of the record during prolonged stimulation of the popliteal nerve, the voltage having been gradually increased whenever the knee jerk reappeared (*e.g.*, from 25 to 27 volts at the arrow). A single shock to the peroneal after 3 minutes' stimulation of the popliteal showed a stronger ipsilateral

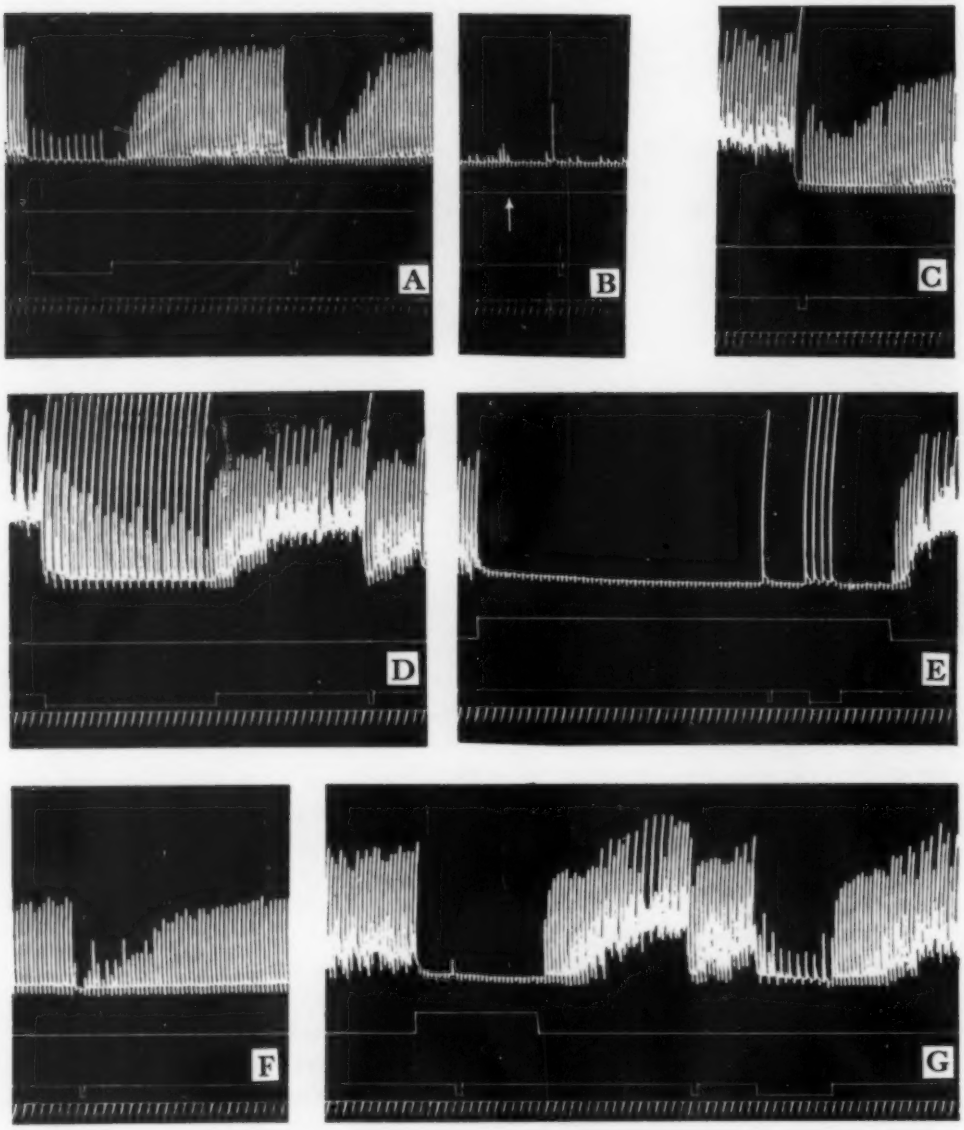

FIG. 3. 2/24/38. Cat, male, 18 hours after transection of spinal cord at T6.

Record as in Fig. 1. Upper signal. Prolonged stimulation of left popliteal, 60 cycle a.c. Voltage increased from 25 to 27 volts at arrow, ↑, in B. 30 volts in E and G. Middle signal. A single shock or a series of shocks at 1 per sec., 66σ before the next succeeding knee jerk to the left peroneal. Photo-electric cell stimulator, 40 volts. Lower signal. Time in seconds. For further description see text.

extensor contraction. C, D and E were recorded 6½ mins. later, during which time two periods of stimulation of 1 min. each intervened. The ipsilateral reponse was much stronger, the inhibition weaker and its after-discharge shorter, particularly during the clonus in D. Thirty-eight minutes without stimulation elapsed between E and F. After this rest period the responses (Fig. 3, F and G) more closely resembled those at the beginning of the experiment (A and B), but the development of clonus and the curtailment of inhibitory after-discharge to a single shock during clonus in G indicated that the activity built up before the rest period had not yet subsided. This illustration was an extreme case, but similar changes of smaller magnitude were common.

A third type of behavior of reflex responses during and following prolonged stimulation was seen less frequently. It usually appeared in preparations in which the general reactivity was low, during the late stages of a long experiment, and in preparations which received barbiturate anaesthetics. In this type of response the ipsilateral extensor contraction was usually absent or, at best, very weak. During stimulation at frequencies of 60 and 120 at voltages of 15 to 30 for as long as 22 mins. there was no reappearance of the knee jerk and at the termination of stimulation there was little or no rebound contraction. The test reflex was essentially unaffected by the prolonged stimulation.

Contralateral extensor and other reflexes. In animals decerebrated by the trephine or anemic methods stimulation of the contralateral nerves evoked a number of reflexes. Extensor contraction was the usual response, but, particularly with the second method of preparation, flexor contraction and inhibition of the extensors with or without rebound contraction were not infrequent. The results of these experiments, as well as of the experiments on inhibition of the contralateral extensor and on facilitation of the contralateral motor cortex by an ipsilateral nerve, may be summarized as follows.

The contralateral flexor reflex behaved in a manner similar to that of the ipsilateral flexor described above. Reflex inhibition of the contralateral extensor showed little tendency to subside during stimulation, but it was not followed by so prolonged a rebound contraction as was reflex inhibition of the knee jerk. Rapid subsidence of the other reflexes during continuous tetanization was rare. In the majority of instances they only partially subsided as long as the afferent nerve was adequately stimulated (frequencies of 30 to 360 were used), and modification of the test reflex continued for periods up to 4 or 5 mins. after the prolonged stimulation was terminated. Changes of long duration, 30 to 40 mins., such as that illustrated in Fig. 3, were not encountered. The modification of the test reflex was always most marked and sometimes only present in its after-discharge.

An example of the responses of the quadriceps to stimulation of contralateral nerves is shown in Fig. 4. The test reflex, A, showed inhibition during stimulation of the contralateral femoral and rebound contraction with relatively long after-discharge. The beginning of prolonged stimulation of the

contralateral sciatic is shown in B with the resulting contraction of the quadriceps. This was not completely inhibited during the test stimulus, but was enhanced by the rebound. Stimulation of the sciatic was continued for 15 mins. between B and C. The prolonged reflex had only partially subsided and there was facilitation of the rebound contraction of the test reflex, though the inhibitory component during stimulation was as complete as in A. Eleven secs. after cessation of sciatic stimulation the inhibitory component of the test reflex appeared unchanged, but the rebound contraction was markedly reduced. In 4 mins. the test reflex recovered.

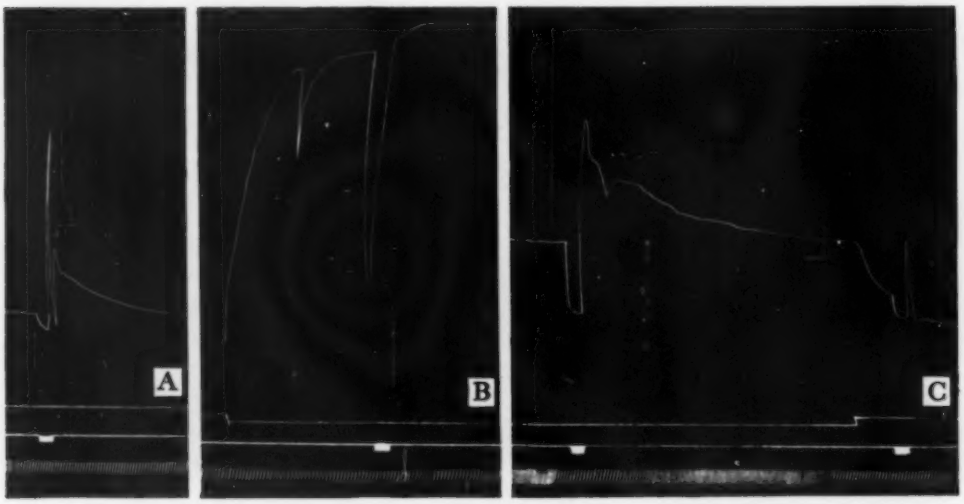

FIG. 4. 9/14/37. Cat, male, anemic decerebration.

Left quadriceps recording. Upper signal. Prolonged stimulation of right femoral. Diphasic shocks, 1σ duration, from the photo-electric cell stimulator through a 1:1 transformer, 45 volts, 60 per sec. Middle signal. Stimulation of right sciatic for 5 second intervals. 60 cycle a.c., 3 volts. Lower signal. Time in seconds. For further description see text.

DISCUSSION

As stated in the introduction, the phenomenon of subsidence of a reflex during continued stimulation has been generally interpreted as being due to a central "fatigue." This sounds plausible, but gives no clue to the nature of the mechanism involved. In a number of experiments (*cf.* those of Upland and Michelson, and also those described on page 536, Fig. 2 above) the subsidence was apparently due to inadequate stimulation, following the change of threshold of the afferent nerve during activity. In other cases, *e.g.*, in the experiment illustrated in Fig. 1, the phenomenon appeared to be due to reflex activity of opposite sign, possibly evoked by different fibers in the mixed afferent nerve. Another example of this is the short maintenance of the flexor reflex under barbiturate anaesthesia, the inhibitory mechanisms being relatively more effective with drugs of this group (Bremer and Moldaver,

1933). It is indeed probable that both of these factors, namely, cessation of activity in the afferent system peripherally, and reflex activity of opposite sign centrally, play a rôle in most if not in all cases of so-called central "fatigue."

In the experiments reported here subsidence of central inhibitory activity only appeared in the presence of a strong excitatory component from the stimulation of the mixed afferent nerve, and "fatigue" or "exhaustion" or reflex inhibition did not occur. This apparent non-fatigability of inhibitory processes does not constitute a qualitative difference between them and the excitatory processes. If it did, one would have to assume that no internuncial neurons were present in the organization involved in reflex inhibition, which is highly unlikely. Further, the experiments on inhibition of the knee jerk (p. 535) showed that the excitatory activity elicited by the prolonged stimulation was as resistant to "fatigue" as was the inhibitory. The observations on the contralateral extensor and other reflexes (p. 539) may be similarly interpreted. The presence of profound inhibition and the absence of excitation in preparations in poor condition or under barbiturate anaesthesia (p. 539) constitute negative evidence with regard to the problem at hand, but suggest differences in metabolic and other chemical properties of the neurons or synapses involved. It may therefore only be stated that in certain reflex systems the central activity, whether inhibitory, excitatory or both, does not subside or "fatigue" as long as the afferent fibers are adequately stimulated for durations of 15 to 20 mins. and at frequencies up to 360 per sec.

The specificity and independence of the afferent paths of the reflex arcs demonstrated by the present experiments may be accounted for by assuming specific and independent internuncial neurons. Moreover, the fact that certain collaterals of the dorsal root fibers end on the anterior horn cells suggests that the synapses are themselves independent units.

No generalization can be made at present about the nature of the reflexes which show rapid subsidence as contrasted with those which do not, or about the properties of the neurons involved in their organization. It is not a function of the dominance of the reflex as measured by its capacity to preempt the final common path, nor a function of the number of synapses in the reflex arc (*cf.* the flexor reflex, which subsides rapidly, and the contralateral extensor, which is well maintained). Certain teleological explanations may be given, but definite data are lacking. In the present series of experiments the reflexes which subsided rapidly were the ipsi- and contralateral flexor and the ipsilateral extensor; those which were well maintained included the contralateral extensor, inhibition of the knee jerk, rebound contraction of the quadriceps following inhibition of the knee jerk, and, in cats under dial, facilitation of the contralateral motor cortex by an ipsilateral nerve.

In conclusion it may be pointed out that, although there appears to be considerable variability in the responses of spinal and decerebrate preparations to stimulation of peripheral afferent nerves, in a long series of experiments these different responses may be grouped into rather specific types.

Among the numerous factors which combine to determine the type of response evoked, the duration and intensity of previous stimulation, hence the technique of preparation, must be considered. The more standardized the technique becomes the more consistent will be the responses evoked, and also, frequently, the more dogmatic the conclusions drawn.

Summary

Certain reflexes of the hind legs of spinal and decerebrate cats, and occasionally of cats under barbiturate anaesthesia, were studied myographically. One afferent nerve was maximally stimulated at frequencies of 30 to 360 per sec. for periods of 1 to over 20 mins. Another afferent was stimulated intermittently in such a manner as to evoke a standard response.

The ipsi- and contralateral flexor and the ipsilateral extensor reflexes subsided completely during the prolonged stimulation. In many cases the standard response was unchanged by the prolonged stimulation, in other cases it was slightly reduced. These results demonstrate a certain degree of independence of the afferent paths of the reflex arcs.

Other reflexes, including the contralateral extensor, inhibition of the knee jerk, rebound contraction of the quadriceps following inhibition of the knee jerk, and facilitation of the response from the contralateral motor cortex by an ipsilateral nerve, showed the same type of behavior on rare occasions. Commonly, however, the reflex did not completely subside as long as the afferent nerve was adequately stimulated. The standard response from the second afferent in these cases showed great variation, remaining unchanged in some but usually being either facilitated or inhibited both during the prolonged stimulation and for periods of 2 or 3 to over 40 mins. afterwards.

It is pointed out that in many cases subsidence of a reflex response is due wholly or in part to inadequate stimulation of the peripheral afferent nerve, or to central reflex activity of opposite sign, and that in certain central nervous system mechanisms reflex activity, both excitatory and inhibitory, continues as long as the afferent nerve is adequately stimulated.

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SEPARATION IN THE BRAIN STEM OF THE MECHANISMS OF HEAT LOSS FROM THOSE OF HEAT PRODUCTION*

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INTRODUCTION

THE MAINTENANCE of a constant body temperature in animals having the power of heat regulation is due to the delicate balancing of activity of two quite distinct physiological mechanisms. One, commonly spoken of as the mechanism of "heat loss" (or "heat dissipation"), prevents undue rise of body temperature by facilitating the dissipation of heat, and possibly also, by reducing metabolic heat. The other mechanism, commonly spoken of as that of "heat production," prevents undue fall of body temperature by increasing the heat produced, as well as by restricting the dissipation of bodily heat. It has often been assumed that the various peripheral structures concerned in each reaction are controlled by the same central mechanism. The alternative possibility of each being to a degree independently regulated by discrete central mechanisms was implicit in Meyer's original hypothesis concerning heat regulation; to quote Hasama:[1] "the thermo-regulatory adjustment of warm blooded animals is affected through a sympathetic thermogenic 'warm center' as well as through a parasympathetic thermolytic 'cold center'." With regard to the central representation of these mechanisms Hasama states, "whether the two are morphologically separable or not we do not know, but they are apparently distinct and discrete functionally, inasmuch as they control each other antagonistically, and thus balance each other."

During the past several years evidence has accumulated which indicates a certain central structural and functional independence of these two mechanisms. I have described various procedures whereby in acute, as well as in chronic, cats and dogs, the mechanisms regulating heat production can be essentially eliminated, leaving certain components of the mechanisms regulating heat loss (panting and vasodilation) still intact.[2,3,4,5,6] The opposite situation, the more or less selective elimination of the mechanisms regulating heat loss with a sparing of the mechanisms regulating heat production, has been described by Bazett, Alpers, and Erb[7] in the cat, Teague and Ranson[8] in the cat, and Ranson, Fisher, and Ingram in the monkey.[9]

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* The acute experiments involving transection at the pontile and thalamic levels were performed in the Laboratory of Physiology, Yale University School of Medicine in 1929–1931. The work based on chronic preparations was carried out in Alabama, and was aided by grants from the Committee on Scientific Research of the American Medical Association and from the Rockefeller Foundation.

The present paper extends my earlier findings with additional observations on the efficiency of the mechanisms regulating heat loss in these preparations, and it supplements the preliminary reports of this early work.[2,3,4]

PROCEDURES

The various surgical approaches to the brain stem and the method of placing lesions have been described elsewhere.[5] The animals' ability to prevent a fall in body temperature was determined by subjecting them to: (i) ordinary room temperatures, (ii) refrigerated box temperature ranging from 0° to 10°C., and (iii) out-of-door extremes during the winter months. Apart from observing rectal temperature under these conditions, observations were also made relative to the presence or absence of shivering. The methods used to test the preparations' ability to prevent a rise in body temperature were exposing them to: (i) a heat beam from an electric heater, (ii) a heated box with a glass door for observation, and (iii) the extremes of warm weather during the summer months. The presence or absence of sweating and of panting were noted under all conditions. During heating tests in the acute experiments, respiratory rates were recorded on smoked paper by means of pneumograph. At the termination of the chronic experiments, as well as in most of the acute, the block of the brain stem containing the lesion was sectioned serially, usually at 10μ, and two alternate series of every 10th section were mounted. One set was stained for fiber tracts by a medullary sheath stain, and the other for cells with cresyl violet.

RESULTS

Medial transverse section of brain stem in upper pons

Acute experiments. In an early series of acute and subacute experiments where bilateral medial transverse lesions of various widths were placed in the brain stem at the level of the pons, it was found that the ability to regulate body temperature was not impaired until the lateral portions of the brain stem were infringed upon.[2] When wider lesions were made, the animals' ability to maintain temperature became progressively impaired and finally eliminated; so long as a narrow strip of tissue remained on both sides, or even on one side, panting could still be elicited. Panting, however, often did not appear until the rectal temperature was raised above normal. The following are briefs of representative protocols.

CAT 107—Operation, Dec. 6, 1929. Following a transverse section (Fig. 1) which cut the entire left medial segment and the greater part of the right medial segment of the brain stem at the middle level of the pons, this cat maintained a normal body temperature for two hours in an icebox at 8°C.; there was conspicuous shivering. When placed in a heated box at 50°C., it did not begin to pant until the rectal temperature reached 40.4°C., at which time typical panting suddenly began and sweat appeared on the pads. The cat was tested on the 7th day after the brain stem lesion.

CAT 117—Operation, Jan. 11, 1930. After a lesion wider than that in Cat 107, but at the same general level (Fig. 1), Cat 117 maintained a normal rectal temperature at room temperature, but it fell from 39°C. to 33.8°C. during a period of 1½ hours in an icebox at 5°C., in spite of the presence of slight shivering. When placed in a heated box at 55°C., it did not pant until the rectal temperature had reached 42.2°C. At this time respiration jumped suddenly from 40 to 150 per min. Two minutes later respiration was 245 per min. The cat was tested on the 3rd day after operation.

CAT 223—Operation, Jan. 18, 1930. Following the lesion which transected the brain stem completely, save for a narrow strip on the left side (Fig. 1) Cat 223 was unable to maintain its rectal temperature at room temperature, since, when removed from the incubator and placed in an ordinary laboratory room, the rectal temperature rapidly fell to 32°C. without any evidence of shivering. In the heated box, respiration jumped suddenly from 42 to 240 per min. when the rectal temperature reached 40.4°C. The cat was tested on the 3rd day after operation.

Chronic experiments. In conjunction with the foregoing acute experiments several questions immediately arose: Was the selective elimination of the mechanism of heat maintenance temporary or permanent in nature? Was a preparation which maintained the ability to pant also able to prevent a rise in body temperature under ordinary conditions of a raised environmental temperature? Were the fibers essential to the panting mechanism limited solely to the extreme lateral segments of the pons? For the solution of these questions it was necessary to turn to chronic preparations. That the heat maintenance mechanism can be permanently and markedly impaired by extensive medial transverse lesions in the upper pons, without materially effecting the heat loss mechanism, is evident from the following experiment (Dog 315-B). The location and extent of the lesion is indicated in Fig. 1.

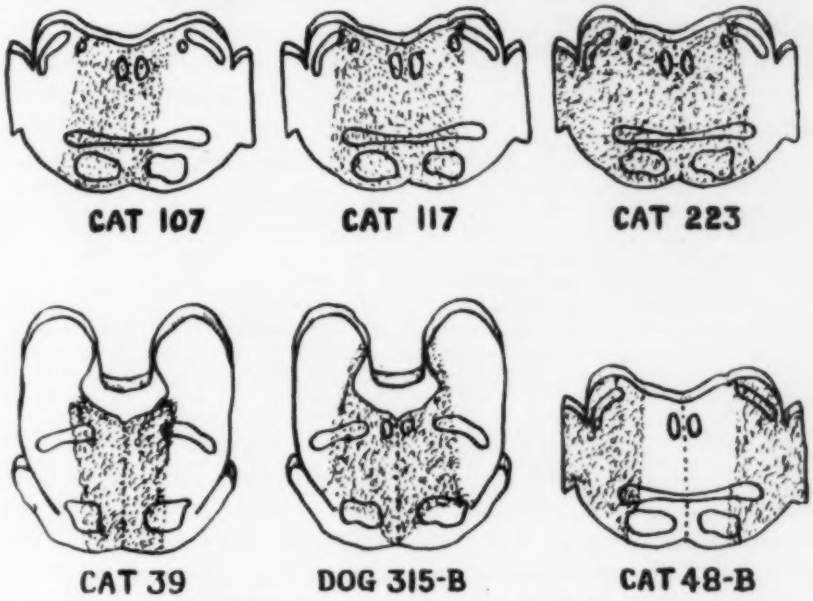


FIG. 1. Drawings showing the location and extent of the lesions in the animals as labeled. For descriptions see text.

DOG 315-B—Operation, May 15, 1934. By means of a bilateral dorsal exposure of the corpora quadrigemina, a straight, blunt probe was projected downward at the midline through the caudal region of the inferior colliculi and cephalic pons until the bone at the base was reached. The probe was then moved laterally through the tissue of the pons, being withdrawn before the most lateral extent of the brain stem was severed. This procedure was first carried out on the left side and then repeated on the right.

In the chronic state this preparation exhibited an inability to maintain a normal rectal temperature at room temperature, but did keep itself somewhat warmer than the environment. Thus during the month of June (beginning 2 weeks after the lesion) it was housed in an ordinary cage in an unheated room. During the night the rectal temperature fell, then rose during the day as the environmental temperature rose. Shivering was never observed even when the rectal temperature reached the low levels of 31.8°, 32°, and 30.5°C. on the 8th, 15th, and 31st days after operation respectively. On the other hand, this dog maintained the ability to pant and to prevent the rectal temperature from rising above a

certain level when subjected to a warm environment. Thus on the 8th day following operation, after being placed in an overheated incubator, vigorous panting began as the rectal temperature reached 40.5°C. The response to the gradual rise of environmental temperature during a warm day is illustrated by its reaction on the 17th day after operation: at 9:00 a.m. the rectal temperature was 38°C., respiration being quiet and regular; at 2:00 p.m. it was 40.2°C.; at 2:40 and at 3:20 the rectal temperature was 39.9°C., typical thermal panting being present periodically. Thus with the onset of panting, a rectal temperature of 40.2°C. was reduced slightly and then maintained, and that without continuous panting. The observations on the 17th day were repeated on several subsequent hot days with the same result. Death occurred the morning of July 2nd (48th day after operation) and a decubitus infection was present. The brain was removed and fixed in formalin. The midbrain-pons block was cut in transverse sections at 20 and every 10th section stained for fiber tracts by the Pal-Weigert method. The lesion had transected the entire brain stem except for the extreme lateral and ventral portions (Fig. 1).

The fact that a lesion must reach well laterally before the mechanisms regulating heat production become impaired was, of course, evident from the acute experiments. This has been verified and emphasized in chronic preparations (cats) having medial transverse lesions at the pontile level. Cat 39 is an example, the location and extent of the lesion being indicated in Fig. 1.

CAT 39—Operation, Dec., 1931. The same operative procedure was carried out as in Dog. 315-B. The lesion was at the same cephalic pons level and was of approximately the same width dorsally (the medial half of both brachia conjunctiva being degenerated), but ventrally the lesion was somewhat narrower than that in the dog. The cat survived until June, 1932. This cat maintained a normal rectal temperature immediately following operation and subsequently, even though it was housed in an open cage in a cold (poorly heated) laboratory during the winter months and was out-of-doors during the early spring. Shivering was prominent. Likewise the cat panted typically and sweated profusely when placed in an overheated incubator on the 22nd day after operation. In addition, it prevented a rise in rectal temperature when out-of-doors during the hot days of an Alabama early summer.

The descending fibers governing heat loss are not confined solely to the lateral segments of the brain stem at the level of the pons because cats, dogs, and monkeys in which the lateral segments were sectioned, leaving the medial segments intact (as indicated by the lesion for Cat 48-B), exhibited no detectable deviation from the normal in heat regulation either in the acute or chronic state.

Transection of brain stem through caudal diencephalon

Acute experiments. After carrying out the acute experiments described above, I endeavored to determine whether the mechanisms regulating heat production could be separated from the panting mechanisms at the level of the hypothalamus.[2] This seemed probable because the polypnea induced by light anaesthesia in normal animals had also been elicited in acute midbrain preparations.[10] In this study some 20 cats were maintained for 3 to 8 days following a complete transection which passed just anterior to the superior colliculi dorsally and through the mammillary bodies ventrally (indicated by line 1, Fig. 2). Without exception, such animals exhibited no ability to prevent a fall in their rectal temperature, it being necessary to house them in an incubator. When removed from the incubator and placed in an ordinary heated

room, their rectal temperatures fell rapidly to low levels and there was no shivering. All except two animals of this group also failed to pant even when overheated to the extent of convulsive prostration at rectal temperatures from 42.5° to 43.5°C. In two animals, however, typical panting was elicited by overheating with a heat beam. One such experiment on a cat is summarized in Table I. It will be noted that although panting was typical, with mouth open and tongue protruding, the maximal rate was slightly submaximal for the normal cat.

In an effort to determine whether transections at higher levels were less prone to eliminate the panting mechanism in the acute state, another series of some 30 cats was studied following transections at various levels of the diencephalon. It was found that when transections passed through the level of the chiasm ventrally (as indicated by lines 2 and 3 in Fig. 2) the animals usually were able to maintain normal rectal temperatures for 24–72 hours (shivering being present) after operation. Nevertheless, overheating these animals to fatal heat prostration failed in most instances to elicit panting. In the preparations in which panting did occur, its onset was definitely delayed until abnormally high rectal temperatures obtained. After its onset the panting was typical and maximal, however, and its abrupt onset was conspicuous.[8]

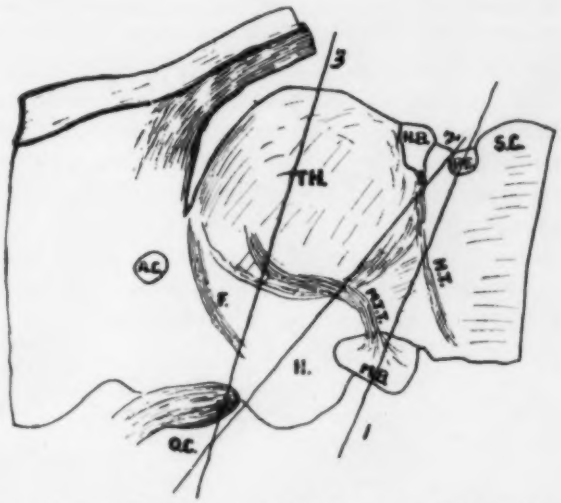


FIG. 2. Drawing sketched from a sagittal section through the diencephalon of a dog. Lines 1, 2 and 3 indicate levels of transections in experiments described in the text. Compare with Fig. 7a.

Table I

Cat 93—Operated upon Oct. 23, 1929
Observations—Oct. 25

Time	Rectal temperature	Respiratory rate	
9:10	38	22	
11:30	38.2	30	
11:34	Heat beam on animal		
11:37		60	
11:40	39.0	90	
11:59	39.8	130	
12:05	40.7	150	Mouth open typical panting
12:13	Heat after water bath	170	Mouth open typical panting
12:16	42.5	150	
12:27	41.3	90	
2:05	36.5	90	

Chronic experiments. The foregoing results on acute material suggested that the essential cephalic brain stem structures which regulate heat production are located rostral to the midbrain. However, the possibility remained that they might be located in part in the cephalic midbrain and only temporarily impaired by the acute lesion. (The failure to elicit panting in the majority of such preparations was interpreted on this basis.) If this were true, some heat regulatory power should return in chronic preparations of this kind. I had had little success in maintaining chronic midbrain animals, *i.e.*, 4 to 6 weeks after operation. Attention, therefore, was focussed upon postoperative care,[6] and specific heating and cooling tests were made only infrequently and for short periods. *It was found (verifying our obseravtions on acute material) that maximal, typical panting is elicitable in the chronic midbrain cat and dog.* In some instances the rectal temperature threshold remained above normal, while in others panting began before any appreciable rise in temperature occurred. Following high transections in the cat, there appeared in the subacute and early chronic state (see protocol of Cat 10 below) some power to prevent a fall in rectal temperature when the animal was subjected to a cool environment.[4] Such a residual power was not present in the dog, at least to the extent seen in cats, following a transection at a corresponding level (see protocol of Dog 289).

Table II. Cat 10

Day after operation.	Rectal temperature. °C.	
14th 9:00 A.M.	39.0	In incubator.
2:30 P.M.	39.2	In incubator.
	Put in refrigerated box.	
2:55 P.M.	38.2	No shivering.
3:25 P.M.	36.5	No shivering.
4:45 P.M.	34.5	No shivering.
5:45 P.M.	31.5	No shivering.
	Removed from refrigerated box.	
24th 7:00 A.M.	38.0	Room temperature 23°C.
9:40 A.M.	38.2	
	Put in refrigerated box.	
11:45 A.M.	36.0	No shivering.
2:00 P.M.	34.0	No shivering.

CAT 10—Operation, Oct. 11, 1932. Complete transection of the brain stem through the cephalic level of the midbrain was attempted through a bilateral dorsal exposure. The lesion was placed by traction with a milliner's needle. Immediately following operation this preparation failed to maintain a normal rectal temperature in the presence of a cool environment and had to be kept in a warm incubator. After 2 weeks it demonstrated considerable power of heat maintenance and could be housed in an unheated cage. Table II shows, however, that it remained unable normally to combat a cool environment. On the 9th day after operation, typical, vigorous, maximal panting was elicited when put in a heated box; its rectal temperature was 41.9°C. and panting appeared abruptly as in other preparations. It was not removed from the heated box until its rectal temperature had reached 43°C.; no sweat appeared on the toe pads, although panting continued uninterrupted. The preparation was again placed in the heated box on the 45th day after operation; at a rectal temperature of 41°C. the respiratory rate was only 66 per min. and 30 minutes later the cat was panting vigorously, the rectal temperature being then 43.8°C. The preparation was then cooled by immersion; exitus occurred the following day.

Sections through the lesion demonstrated that the transection was complete at the

level of the posterior commissure dorsally and the mammillary body ventrally except for a small tag of dorsal tissue on the left side into which the posterior commissure ended (Figs. 3a and b).

DOG 289—Operation, Apr. 17, 1934. Complete transection of the brain stem through the cephalic level of the midbrain was attempted via a bilateral dorsal exposure. Following operation this dog failed to maintain its rectal temperature which was 28.5°, 29.2°, 30° and 28.5°C. on the 1st, 3rd, 12th, 18th, and 28th days after operation respectively. It was necessary to house this dog in an incubator during its entire postoperative course. Shivering was never observed. The dog was tested for panting on the 28th day after operation. At this time typical panting at a relatively slow rate (105 per min.) was elicited in an incubator when the animal's rectal temperature was 38°C. The dog was removed from the heated box and *respiration continued at a rapid rate for some time in spite of a fall in the rectal temperature.* On this same day it was placed outside in the sun. Typical rapid panting ensued, at a rectal temperature of 38.2°C. The following morning the dog began vomiting spontaneously and was sacrificed. The location and extent of the lesion is shown in Fig. 3. e-h.

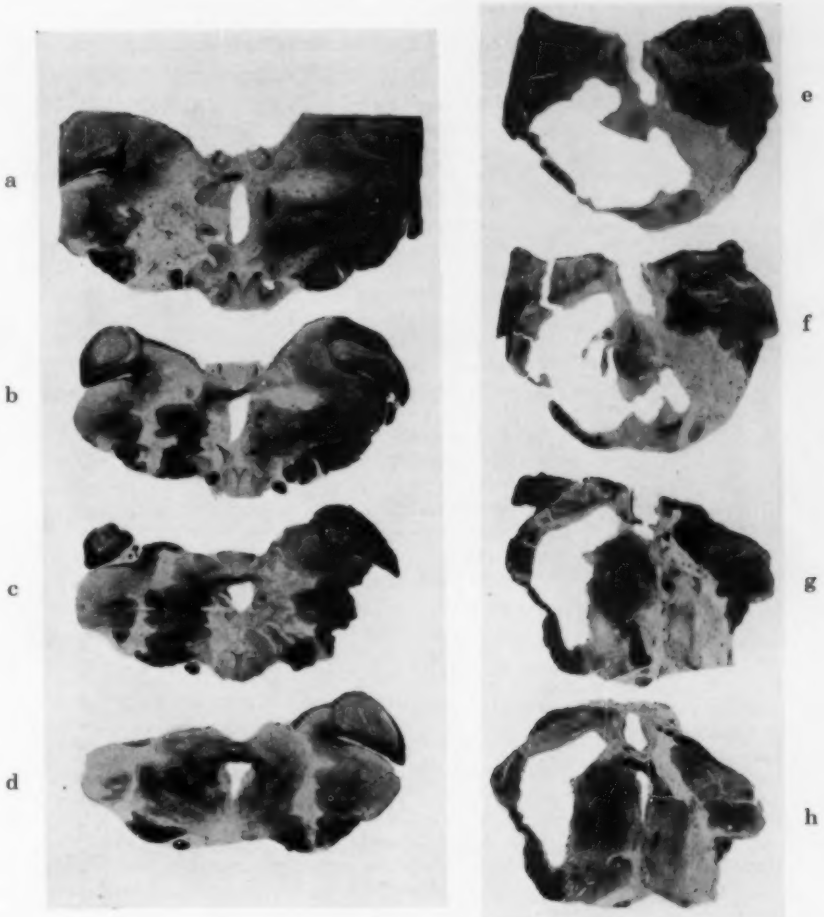


FIG. 3. a-d are photomicrographs of cross sections from the series on Cat 10. Note completeness of transection except for dorsal medial tag on left side. e-h are photomicrographs of cross sections from the series on Dog 289. Note completeness of transection.

Isolation of the hypothalamus

Acute experiments. The elimination of the mechanisms regulating heat production with sparing of the panting mechanism was particularly well demonstrated in acute preparations in which the hypothalamus was either completely isolated by a narrow lesion from the rest of the brain stem or its dorso-caudal connections were severed.[3] In certain of these preparations vigorous, typical panting was readily elicited in spite of the animals' being in a cool environment with a normal or even an extreme subnormal rectal temperature. Stimuli which normally are not concerned with, or at least are not adequate to excite, panting elicited polypnea with ease. Thus movements of the animal, passive or spontaneous, such as: arousal from sleep, urination or defecation, massage so slight as pinching the tail, activated the polypnea mechanism. In addition, *these preparations exhibited continuous visible dilatation of the ear vessels.* The following briefs from protocols are representative.

CAT 61—Operation, Feb. 8, 1932. An attempt was made to sever the hypothalamus from the lower brain stem by "over-cutting" its caudal, dorsal, and cephalic connections with a small blunt probe. No surface bleeding occurred.

Postoperative notes. The cat's temperature was maintained near normal in an incubator at 30°C. for the first 3 days after operation. On the 3rd evening the incubator was cooled to 24°C. The following morning the cat's rectal temperature was 28°C. There was no shivering. On the 5th morning the rectal temperature was 31°C., with the incubator at 27°C. There was again no shivering. Respiration at this time was fast, and pneumonia was suspected; the blood vessels of the ears were dilated. On the 8th day respiratory rate of the undisturbed animal was 36 per min. and rectal temperature 34°C.; when picked up it promptly began typical panting. The ear vessels were again dilated. On the 11th day, pneumonia not having developed, the animal's reaction to overheating was tested. At 1:30 p.m. it was placed in an incubator at 35°C. Its rectal temperature was 34.4°C. and its respiratory rate was 100 per min., when typical panting was present after handling. At 1:45 p.m. the cat had become quieter in the incubator and was breathing 75 times per min. At 2:00 p.m. respiration was 130 per min., the mouth was not open, *i.e.*, panting was not yet present. At 2:10 the cat was panting vigorously and typically, the mouth being open and the tongue protruding. The respiratory rate was over 180 per min. and rectal temperature 39.2°C. The cat had not gotten to its feet or moved except to stretch; *panting in this instance was, therefore, elicited normally by heating.* At 2:35 the rectal temperature was 41°C. and the cat was still panting vigorously. On the 13th day temperature was 32.5°C. with no shivering; at 7 p.m. on this day the preparation was found dead.

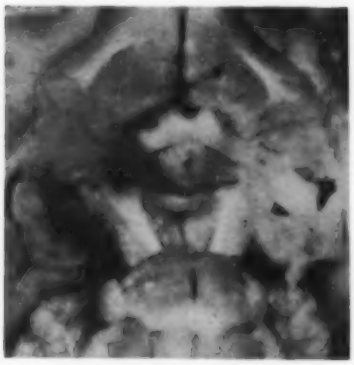


FIG. 4. Photograph of the brain of Cat 61 showing the surface boundaries of the lesion. Note that the hypothalamus is isolated from surrounding tissue. Also, that the isolated hypothalamic tissue exhibits no softening.

At autopsy the lungs were normal. The brain was clean and after the pia was stripped the lesion was readily seen (Fig. 4) to pass well ahead of the optic chiasm anteriorly and through the anterior extent of the mammillary bodies caudally. Serial sections of this region revealed that the dorsal extent of the lesion encroached slightly upon the ventral portion of the thalamus. The whole of the hypothalamus except in its most caudal extent (caudal half of the mammillary bodies), was completely separated from the lower brain stem. The separated tissue still maintained its blood supply since there was no softening evident; likewise there were no thalamic infarcts.

CAT 111—Operation, May 18, 1932. The hypothalamus was isolated as in Cat 61, after which it was macerated with forceps.

Postoperative notes. The morning after operation, respiration was rapid, being 108 per min. when the cat was resting. The ear vessels were markedly dilated, and massaging did not elicit panting. On the 2nd postoperative day the respiratory rate was 150 when the cat was resting in an incubator at 27°C. and rectal temperature 36°C. The ear vessels were dilated and massage of the animal elicited typical panting. On the 3rd morning the cat was panting typically with a rectal temperature of 37°C., being housed in an incubator at 31°C. The cat was sacrificed on this day by administration of nembutal. The lungs were normal and the brain clean except for subpial blood stains on the right temporal pole. The region of macerated hypothalamus was filled with clotted blood (Fig. 5). There were no thalamic infarcts.

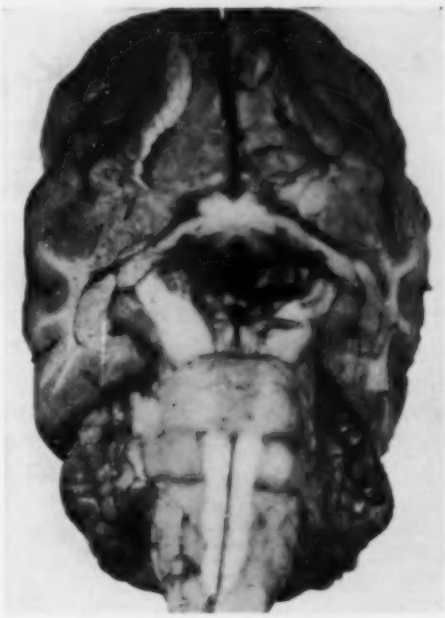


FIG. 5. Photograph of the brain of Cat 111. Note the absence of the hypothalamus and its replacement with clotted blood.

CAT 112—Operation, May 6, 1932. The hypothalamus was first isolated from its dorso-caudal connections and then the hypothalamic tissue was macerated with forceps. No hemorrhage occurred.

Postoperative notes. The morning after operation the cat's rectal temperature was 28°C. and on the 5th morning, 30°C. There was no shivering. At rest its respiratory rate was 150 per min., but the mouth was not open in the panting attitude. As the cat stood up and began urinating, it suddenly began panting vigorously and typically. The ear vessels were moderately dilated. The cat subsequently, until death on the 8th day, maintained a constant picture. It exhibited no evidence of being able to maintain its rectal temperature or to shiver. The ear vessels were continually dilated. Respiration continued rapid even when resting, typical panting always occurred when the animal was handled or moved spontaneously. The whole of the hypothalamus was involved by anemic necrosis without infringement upon the thalamus, except the most ventral portion (Fig. 6).

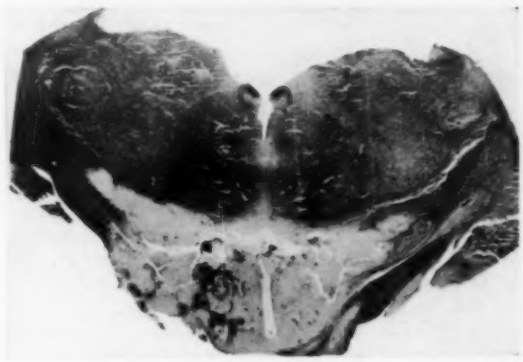
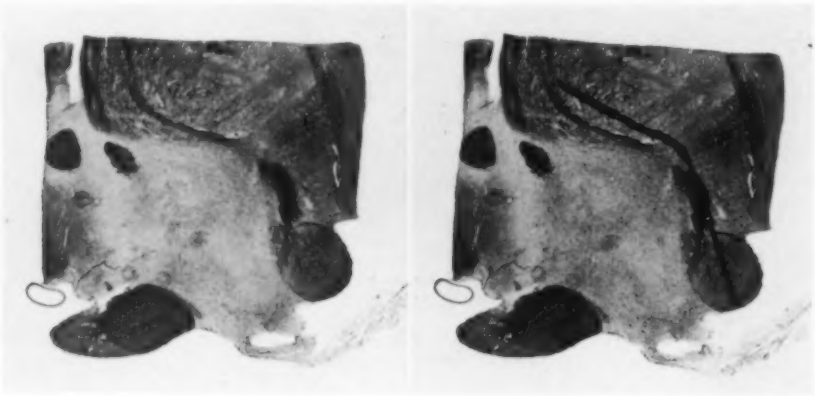


FIG. 6. Photograph of a cross section at the level of the hypothalamus from the series on Cat 112. Note the entire hypothalamus is involved by anemic necrosis.

Chronic experiments. A persistent absence of the mechanisms regulating heat production with a sparing of those regulating heat loss has been encountered in several dogs, maintained to chronicity, in which the dorsocaudal connections of the hypothalamic grey were severed. Such dogs in the acute state exhibited an inability to regulate against a lowered environmental temperature, but in the chronic state some residual thermogenic power was evident. Thus, sev-

eral days after operation, when these animals were transferred from the incubator to room cages, the rectal temperatures remained low (32° to 34°C.), but above the values for acute midbrain dogs maintained under the same conditions. When subjected to cool environments, the rectal temperatures fell progressively and shivering did not occur. Typical panting was elicited by warm environments at normal rectal temperatures and, in addition, *the animals exhibited the ability to prevent a rise in body temperature when subjected to ordinary over-warm environments.*

In certain of these dogs there was an increased susceptibility to polypnea (as in cats), which made its appearance either immediately after operation or several days later and persisted indefinitely. The heat loss mechanisms (vasodilatation of ear vessels* and panting) were most frequently released by lesions which roughly followed the course of the mammillo-thalamic tracts in the hypothalamus. In the animals with a more caudal section (midbrain dog), this increased susceptibility to panting was seen only infrequently even though the heat loss mechanisms still appeared to react normally to over-heating. The following are briefs from the protocols of 2 dogs having the dorso-caudal hypothalamic connections severed (Fig. 7).



a b

FIG. 7a. Photomicrograph of a sagittal section through the diencephalon of a dog, showing the demarcation of the hypothalamic grey. b. The same photomicrograph with the location and extent of the lesion in Dog 116-C indicated by an inked line.

* This persistent vasodilation (ear vessels) is not the simple equivalent of removing the source of the vasotonic impulses, *e.g.*, as when the cervical sympathic trunk is cut. This is shown by the fact that vasodilation is not present in low midbrain, pontile, or high medullary preparations, nor is it present (including the other components of Horne's syndrome as determined by ordinary methods of observation) following unilateral removal of the hypothalamus or hemisection of the brain stem at a midbrain, pontile, or upper medullary level. Unilateral vasodilation does occur following hemisection of the lower medulla, but it is not as lasting as that which follows section of one cervical sympathic trunk. Therefore, the bilateral vasodilation which follows severance of the hypothalamus from the lower brain stem is peculiar to a bilateral lesion at this level, and is interpreted as being primarily associated with the activation or release of the heat loss mechanism (unpublished observations).

DOG 116—Operated upon June 12, 1936. After elevation of the temporal pole, the probe was projected through the pia just back of the optic tract at the point of its contact with the cerebro-spinal tract. As the probe was pushed into the brain tissue, its point was turned dorsally so as to infringe upon the thalamus and to spare the dorsal hypothalamic fibers. After the probe had reached the opposite side it was pulled gently caudad and ventrad to sever all caudal hypothalamic connections.

Postoperative notes. This dog immediately after operation exhibited an inability to prevent a fall in rectal temperature when housed in an ordinary heated room (Table III). At the end of two weeks it showed some residual powers in this respect. Subsequent to the appearance of spontaneous panting, this residual power was undoubtedly masked to some extent by heat loss due to the panting.

On the *14th day* slow panting was observed, with mouth open and tongue out. The dog was standing, and the rectal temperature was 33.5°C. Previous to this, respiratory rates were not recorded, but no deviation from the normal had been noted. At 10:30 P.M. the dog was observed while sleeping. Respiration was slow (8 per min.) but regular. The animal was then placed on the floor, whereupon it began to walk and at the same time to pant slowly; gentle massaging readily elicited rapid, vigorous panting which continued until some time after the dog had become quiet. As soon as the animal was aroused or moved spontaneously (to urinate or defecate) typical polypnea ensued, regardless of the environmental or body temperature.

In response to an over-warm environment (31–32°C.) on the 24th day, during which the animal lay undisturbed (thus ruling out polypnea from activity) the rectal temperature rose progressively over a period of 6 hours from 32° to 38°C. and was maintained at this level for 3 hours. Typical panting began more or less abruptly when the rectal temperature reached 38°C. and continued during the remaining period of observation.

Death occurred on the 30th day from fluid aspiration. The lesion reached well dorsally into the thalamus at the caudal level of the optic chiasm. At the midlevel of the hypothalamus it cut directly across the ventral extent of the thalamus just above the mammillo-thalamic tracts. From here the lesion turned sharply downward, passing just caudal to the mammillo-thalamic tracts. Thus all the fibers taking origin from, or passing through, the hypothalamus ventral and anterior to the mammillo-thalamic tract were severed. There was no softening of the isolated hypothalamic tissue (Fig. 7).

Table III. Dog 116-C

Day after operation.	Rectal temperature. °C.	Environmental temperature. °C.
2nd 9:00 A.M.	30.0 No shivering.	23
6th 9:00 A.M.	30.5 No shivering.	23
10th 8:00 A.M.	34.0 No shivering.	27
16th 8:00 A.M.	34.0 No shivering.	24 After massage, typical panting.
21st 10:00 A.M.	33.0 No shivering.	26 Spontaneous panting.
26th 9:00 A.M.	32.0 No shivering.	26 Spontaneous panting.
29th 10:00 A.M.	31.0 No shivering.	26 Spontaneous panting.

DOG 117—Operation, June 15, 1936. The same operative procedure was carried out as in Dog. 116.

Postoperative notes. This dog was first maintained in a heated incubator for a few days, then in an unheated one for a like time and finally in an open cage at room temperature near 25°C. The dog never maintained its rectal temperature, as is evident by the following recordings:

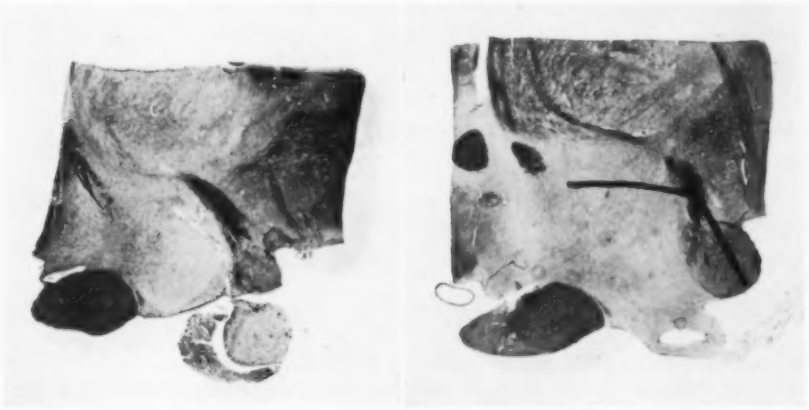
4th day—31.5°C.
7th day—32.5
14th day—31.5
21st day—32.5
29th day—32.0

Shivering was never observed. On the 2nd day the dog's rectal temperature was *accidentally raised to 40.2°C. and panting did not occur.* On the 21st day reaction to an over-warm environment was tested under the same conditions as Dog 116. Done simultaneously the rectal temperature rose progressively from 32° to 38.5°C. (environmental temperature from 25° to 31–32°C.) at which time panting began and continued periodically during the remainder of the test. Immediately with the onset of polypnea the rectal temperature was reduced to, and maintained at, 38°C. Previous to this test this dog displayed no increased

tendency to polypnea. Subsequent to the test, however, it exhibited a definitely increased tendency to pant; thus, on the 25th day vigorous panting occurred with a rectal temperature of 35°C. and again on the 27th day with a rectal temperature of 34°C. On both occasions the humidity of the room was high and the dog was walking around. It is not clear, therefore, whether panting in these instances was due to an increased susceptibility to heat or a result of activity, as in Dog 116. It was suspected that the latter was the case. In any event, the animal became more sensitive after its experience on the 21st day.

Death occurred on the 30th day from a jaw infection. The lungs and trachea were clean. The experimental lesion passed just dorsal and caudal to the caudodorsal and caudal extent of the mammillo-thalamic tracts and was like that in Dog 116, except that it did not reach as far anteriorly and dorsally. There was also a sizable anemic infarct in the thalamus on the right side (Fig. 7).

Dogs in which the lesions fell short of isolating the whole of the hypothalamic grey exhibited normal power of regulating its heat production in the chronic state. Lesions of this type are shown in Fig. 8. The photomicrograph shown in Fig. 8a is of a section from the series on Dog 102-C. This dog was operated upon in April, 1936, and sacrificed three months later. The line in Fig. 8b indicates the dorso-caudal borders of the lesion in Dog 398-B, operated upon in July 1934, and surviving three months. Most of the hypothalamic grey anterior and ventral to the black line was involved by lesion scar. These dogs, as is typical following such lesions, ran slightly subnormal rectal temperatures for several days after operation but subsequently exhibited no deviation from the normal either when subjected to low (refrigerated box at 5°C.) or high (out-of-doors in summer at 30–35°C.) environmental temperatures.



a b

FIG. 8a. Photomicrograph of a sagittal section from the series on Dog 102-C. Note that the lesion passed just anterior to the mammillo-thalamic tract, and did not reach through the uppermost extent of the hypothalamus. b. A sagittal section through the hypothalamus with the dorso-caudal extent of the lesion in Dog 398-B indicated by an inked line.

DISCUSSION

The permanent impairment of the mechanisms regulating heat production, caused by wide, medial transverse lesions at the upper level of the pons (Dog 315), is probably to be interpreted as due to the severance of descending fibers

normally essential to this function.* If this is correct, it is evident that these fibers (descending from neural elements located in the posterior hypothalamus) have a wide-spread distribution at the level of the pons. This is in general agreement with conclusions drawn by Magoun, Ranson and Hetherington.[11] The ability to maintain a normal rectal temperature and to shiver when subjected to a cool environment was not eliminated by medial transverse lesions until they reached well laterally (Cat 39) nor by lateral transverse lesions on both sides so long as strips of medial tissue remained unsevered (Cat 48). Shivering is, however, eliminated by medial transverse lesions before elimination of the mechanisms of metabolic heat liberation, indicating more lateral distribution of the latter fibers. The experiments do not give information regarding the relative density of fibers in a pontile cross-section, since nothing is known regarding the number that can be destroyed without showing a deficit in function. The experiments do demonstrate, as would be expected, that there is an enormous reserve in this respect. It is quite possible, therefore, that the fibers subserving the mechanisms of heat production are actually more numerous medially than they are laterally, as Beattie, Brow and Long[12] found for fiber degeneration following posterior hypothalamic lesions. It is likewise evident that the fibers descending from the cephalic mechanisms controlling heat loss also have a wide distribution at the level of the pons, since the power to prevent a rise in body temperature is not eliminated either by extensive bilateral medial or lateral transverse section. Our evidence indicates that the power to prevent a rise in rectal temperature is impaired before the power to prevent a fall when lateral lesions infringe upon the medial reticular areas. This suggests that the heat loss fibers are sparse in the tissue immediately adjacent to the midline, at the level of the pons. Peet and List,[13] on the basis of clinical material, suspect that the descending fibers controlling sweat secretion also have a lateral course at this level.

The failure of chronic midbrain cats and, especially dogs, as well as animals with dorso-caudal hypothalamic connections severed, to regulate adequately against a fall in body temperature indicates that the bulk of the essential cephalic neural elements are actually confined to the hypothalamus in these species. Cat 10 (high midbrain) in the chronic state possessed considerable power to prevent a fall in rectal temperature when subjected to low environmental temperatures.[4] Thauer and Peters[14] have shown this to be true, possibly to a more marked degree, in the rabbit, although Cat 10 is essentially identical to Rabbit 89 of their series. To a lesser extent, dogs in which only that portion of the hypothalamus caudal to the mammillo-thalamic tracts remained connected with the midbrain (Dogs 116 and 117) also maintained their rectal temperature. Since the midbrain dog (Dog 289) failed to display this residual power, it may be that a progressive encephalization of these

* It is recognized that at times the rectal temperature is maintained in varying degrees, with frequent uncontrollable hyperthermias, following complete transection of the brain stem at the level of the pons in the cat (Keller, A. D. and Hare, W. K., *Proc. Soc. exp. Biol. N. Y.*, 1932, *29:* 1167) and dog. It has not yet been determined whether this is due to a release of subsidiary mechanisms or to an abortive stimulatory effect.

elements occurs in the rabbit, cat, and dog. In any event, the question arises whether this residual power of heat maintenance is due to the recovery, during the subacute state, of cells caudal to the lesion normally concerned with this function or to the released activity of lower subsidiary mechanisms. The first alternative seems the most probable.

On the basis of acute experiments, I am in agreement with Bazett, Alpers, and Erb[7] and Teague and Ranson[8] that the anterior hypothalamus is not essential for the adequate regulation of body temperature against low environmental temperature. Furthermore, the ventral two-thirds of the hypothalamic grey can be separated or destroyed in the dog and cat (Dog 398: Fig. 8) without permanently eliminating this mechanism.[4] The elicitation of typical thermal *panting* in acute midbrain preparations as well as in animals with the hypothalamic connections severed demonstrates that the hypothalamus is not essential to this function. Further, since such preparations in the chronic state possess the ability of preventing a rise in body temperature, it is evident that this function in these circumstance is likewise independent of the hypothalamus. Whether or not avenues of heat loss other than those of panting and vasodilation were utilized in attaining this end is not yet clear. Visible sweat was not observed in these preparations. The recent work of Ranson, Fisher, and Ingram[9] suggests that the cephalic representation of the sweat glands is confined to the hypothalamus in the monkey. This may likewise be true in the dog and cat. In this connection, it is to be borne in mind that the work of Hasama[1] and Magoun, Harrison, Brobeck and Ranson[15] make it seem certain that the cephalic (brain stem) representation of the mechanisms controlling heat loss extends upward into the hypothalamus.

The fact that the mechanism regulating heat loss carries on adequately in preparations in which the mechanisms controlling heat production have been virtually eliminated, bears ample evidence of functional *independence* of the former from the latter. In spite of this, a reciprocal innervation between the two mechanisms is to be expected. The striking release of the panting and vasodilator outflows in certain of the anhypothalamic and midbrain preparations may be evidence of such a relationship. It is more specifically shown in preparations in which thermal panting was elicited only when the rectal temperature reached the normal panting level, yet continued for some time after the rectal temperature was again reduced below normal (see protocols of Dog 289 and Cat 61). Thus, in these preparations the mechanism for activating the heat loss outflows is essentially normal, but that for arresting their activity is partially impaired. Whether or not the increased susceptibility to panting at low rectal and environmental temperatures is a result of the absence of a normal reciprocal innervation between the two mechanisms, this phenomenon must be due to some sort of released activity because it continues into the chronic state. An irritative effect would be present only in the acute and subacute states. This increased susceptibility to polypnea encountered in our preparations (1932) is undoubtedly the same phenomenon described by Lilienthal and Otenasek[16] and termed by them "decorticate polypneic panting" (1937).

Summary

In the cat and the dog the mechanisms controlling heat production can be virtually eliminated, while sparing the mechanisms regulating heat loss, by the following procedures: (i) severing all descending fibers except those in the outer extent of the lateral reticular formations by a wide medial transverse lesion at the upper pontine level, (ii) complete transection of the brain stem through the caudal extent of the diencephalon, and (iii) severing the dorsocaudal hypothalamic connections.

The structural elements subserving the mechanisms of heat loss and heat production in the *cephalic brain stem* have separate anatomical loci, the former extending further caudally than does the latter. Further, the fibers descending from the mechanisms controlling heat loss have a slightly greater lateral distribution at the level of the pons than do those involved in heat production. Both sets of fibers are widely distributed at this level.

Although activation of the heat loss and the heat production mechanisms is quite independent, a reciprocal innervation, nevertheless, exists between the two.

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ANOXIA AND BRAIN POTENTIALS

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MANY METHODS for determining the absolute and relative oxygen requirements of different parts of the nervous system depend on recognition of structural or functional changes which follow deprivation of the normal oxygen supply. Since it is generally believed that the structures with the highest respiratory rates suffer most rapidly from oxygen want, three *time* parameters can be used to obtain quantitative evidence of relative oxygen requirements (Gerard, 1938a, b); (i) survival time, *i.e.*, the duration of anoxia required to bring about the change in question (*e.g.*, loss of response, histologic alteration); (ii) revival time, *i.e.*, the duration of anoxia which still permits reversal of this change when oxygen is restored; and (iii) recovery time, *i.e.*, the interval between readmission of oxygen and start of restoration to normal.

Anoxia of the brain *in situ* may be produced suddenly by quick occlusion of arterial blood flow. Using rabbits, Astley Cooper, in 1836, first blocked both carotids and vertebrals, and observed muscle spasm and respiratory failure, and similar though milder changes in dogs (because of their richer anastomoses). This work has been extended to other animals (Hill, 1900; Pike, Guthrie and Stewart, 1908a; Gildea and Cobb, 1930), and to the resuscitation of the head and brain by perfusion of the isolated head (Hayem and Barrier, 1887; Pike, Guthrie and Stewart, 1908b; Crile and Dolley, 1906; Heymans, Jourdan, and Nowak, 1934); and anaemic decerebration has been introduced (Pollock and Davis, 1923; Swenson, 1925; Kabat and Dennis, 1938). The differential effects of anoxia have been investigated further by studying, during or after anemia, histological changes (Gomez and Pike, 1909; Gildea and Cobb, 1930), conditioned reflexes (Andrejev, 1935,a,b), reflexes of the brain stem (Heymans and coworkers, 1934, 1935, 1937), and changes in chronaxie (Rizzolo, 1927; Richard, 1936; A. and B. Chauchard, 1936). Of these methods, only the histological approach lends itself to fine localization and even this is unsuccessful when applied to the brains of animals dying during, or soon after, acute anaemia (Gomez and Pike, 1909).

The newer electrical techniques offer a better means of following continuously the influence of anoxia on specific brain regions. Prawdicz-Neminski (1925) obtained waves of 11 to 16 per sec. from the motor and visual cortices of curarised dogs, with the string galvanometer, and followed changes in them after suspending artificial respiration. The potentials did not alter during the (estimated) dyspnoea phase of asphyxia; they increased through the convulsive phase but reached a maximum, at 3 minutes, after convulsions ceased, and finally disappeared in 5 minutes, though the heart continued to beat. This refuted the contention (Tchiriev, 1904) that brain potentials were due to movement of blood and lymph. Bartley and Bishop (1933) reported a periodic

paling and flushing of the cortex associated with a decrease and increase of potentials, and a complete absence of potentials 3 to 5 minutes after ligating a superficial artery supplying the area under observation. Bilateral carotid occlusion abolished the 8 to 18 per sec. potentials from the cat's motor cortex in 20 sec. (Simpson and Derbyshire, 1934). One of their records (in Gibbs, Davis, and Lennox, 1935) shows return in 30 secs. after release of a 60 sec. occlusion. The occipital cortex showed less change, attributed to circulation through the vertebrals.

The human EEG was reported (Berger, 1934) to become more regular and with larger waves, rather suddenly, after about seven minutes rebreathing from a closed bag with CO_2 absorbed. Breathing mixtures of low oxygen pressure slows and diminishes the 10 per sec. waves in man (Davis, Davis, and Thompson, 1938) leading ultimately to loss of all activity or appearance of the slow "delta" waves. Potentials of the "isolated" cat brain (severed at the pons, Bremer, 1935) are affected in 12 secs. after ceasing artificial respiration and gone in 40 to 50 secs. (suprasylvian gyrus, Bremer and Thomas, 1936), to reappear within 3 secs. (Bremer and Thomas, 1936; Fig. 1E) after respiration is resumed. Thalamic potentials are lost in 60 secs. following simple carotid occlusion (Dubner, unpublished). A sufficient fall in blood pressure, produced by raised pericardial pressure (Beecher, McDonough, and Forbes, 1938) or by peripheral vagus stimulation (Bailey and Bremer, 1938), likewise eliminates cortical potentials in the cat.

In many of the studies cited, anoxia has been far from complete, due to continued vertebral and other circulation, and times from interference with respiration or oxygen supply to changes in brain potentials do not, of course, give the survival time for brain structures but this plus an unknown duration of diminishing oxygen delivery to them. Further, no comparative values for various brain structures are available. It was our intention, therefore, to obtain records of potentials from a number of regions and to follow quantitatively the changes induced in them by abrupt and complete stoppage or release of the blood flow; in the hope that these survival and recovery times could be related to other data indicating the relative respiratory requirements of brain structures.

METHOD

Cats were anaesthetised with nembutal (30 mg. per kg. intraperitoneally), a tracheal cannula inserted, lifting ligatures placed on both carotids, and the vertebrals exposed and ligated. In the cat, complete interruption of the carotid and vertebral circulations (verified at autopsy) leads to respiratory failure in 30–40 secs., preceded by variable tonic and clonic contractions; and such failure after occluding the carotids temporarily was taken as an indication of the successful elimination of all vertebral flow. The control is important, for accessory vertebrals are common, especially on the left side, and as many as three vessels on one side and two on the other have been encountered in three animals. Sometimes it was necessary to ligate the vertebrals at their origins, after dissecting along the subclavians; usually exposure between the longus colli muscle and the 7th and 8th cervical roots was sufficient.

The animal was now turned over, the head elevated, and extensive removal of the left side of the calvarium achieved with relatively little bleeding. The Horsley-Clarke instrument was then attached. Concentric or bipolar leads fed potentials through a push-

pull, resistance-capacity coupled amplifier into a crystograph, loud speaker, and cathode ray oscillograph. Two channels were usually used, a lead from the motor cortex serving as a standard of reference for another one which was moved about at intervals. The cortex was carefully kept warm and moist with ringer-soaked cotton and the scalp wound was closed with clips between adjustments of electrodes.

Finally, the right (contralateral) carotid was ligated, and the thread about the left one led into a glass tube so that it could be occluded by traction without otherwise disturbing the animal or producing an electrical artifact. Anaemia periods of 20–180 secs. were used, usually not repeated within ten minutes of a preceding one. Observations began three to four hours after anaesthesia was induced and when the anaesthetic effect had largely worn off. When repeated anoxia had modified the preparation too much, after several hours, the head was perfused with Ringer followed by 10 per cent formalin, and allowed to harden. The electrode positions were checked by gross section, the needle track being well marked and its deepest point taken. Agreement with the Horsley-Clarke coordinates (Gerard, Marshall, and Saul, 1936) was usually good.

Results

Satisfactory experiments were performed on 15 cats, with many observations from each of several regions. The usual signs of brain anaemia were regularly observed: first increased respiration (usually immediate in onset) followed by general tonic and clonic movements (from the 20th to the 60th sec.), then progressively diminishing breathing and movements ending in apnoea and flaccid areflexia (30 to 40 secs. for cessation of respiration; 60 to 70 for passive posture). A comparable sequence is manifest in brain potentials, which will be described first as typical of the motor cortex. Special variations will be considered later.

In the motor cortex (Fig. 1), high frequency waves appear or increase in speed and amplitude from one or two seconds after cessation of respiration until 10 or more. By 12 secs. all fast waves have disappeared, and the slower ones (1 to 3 per sec.) by 20. The record remains flat for the remainder of a 29-second anaemia period. Five seconds after restoring blood flow, electrical activity is ushered in by low irregular waves, with a spindle of 6 to 9 per sec. starting at the ninth second and lasting nine more, gradually fading into a new abruptly starting spindle of considerable regularity. Fast waves soon appear, and are partly superimposed on other spindles, which continue to reappear with diminishing amplitude and regularity and with increasing wave frequency (10 to 12 per sec.) and longer intervals between groups until, by four to six minutes, the normal appearance of continuous rapid waves or rapid waves and spindles is established.

The post-anaemic spindles are especially characteristic and also vary most consistently with the duration of the anaemia period. With longer occlusion, the spindles begin later after release and are individually longer (compare the values for a 235 sec. occlusion with those above for a 29 sec. one: the first spindle began 33 sec. after release and continued for 40 sec., instead of 9 and 9). In fact, as shown in Fig. 2, there seems to be a linear relation between occlusion time and recovery time. Furthermore, the spindles usually start at slow frequencies and finish with rapid ones (variations from 6 per sec. to 12 per sec. have been found between the beginning and the end of long spindles). These relatively slow waves follow anaemia even though fast waves only were

discernible in the preocclusion record; when the preocclusion record contains spindles, these are usually smaller than the postocclusion ones. (This enhancement of existing rhythms has been found also in the geniculate body and the cerebellar grey.) The beginning and ending of spindles may be gradual or abrupt: usually the first postanaemic one has a gradual start, while the ones which follow become increasingly abrupt (Fig. 3).

Fast potentials, throughout the brain, are more susceptible to anaemia than slow ones. After an initial increase, they disappear before the slow; they return later when circulation is restored; and they are abolished irreversibly after repeated anoxia periods when the slow waves may show no measurable modifications. Slow waves from the medulla and cerebellum are so resistant to anaemia that they often remained at the end of an occlusion lasting two to three minutes, although the fast oscillations were gone in 40 or 10 secs., respectively. Bursts of rapid waves often appeared late in these regions, however, and might be seen for 4 to 6 sec. periods as late as one minute after occlusion. The possibility that these variations might be due to incomplete anaemia could not be directly attacked, but the criteria of anaemia were satisfied in these animals (including the disappearance of simultaneously recorded potentials from the motor cortex, and the complete disappearance of potentials from other regions in the medulla and cerebellum).

The obex region of the medulla has commonly developed a special

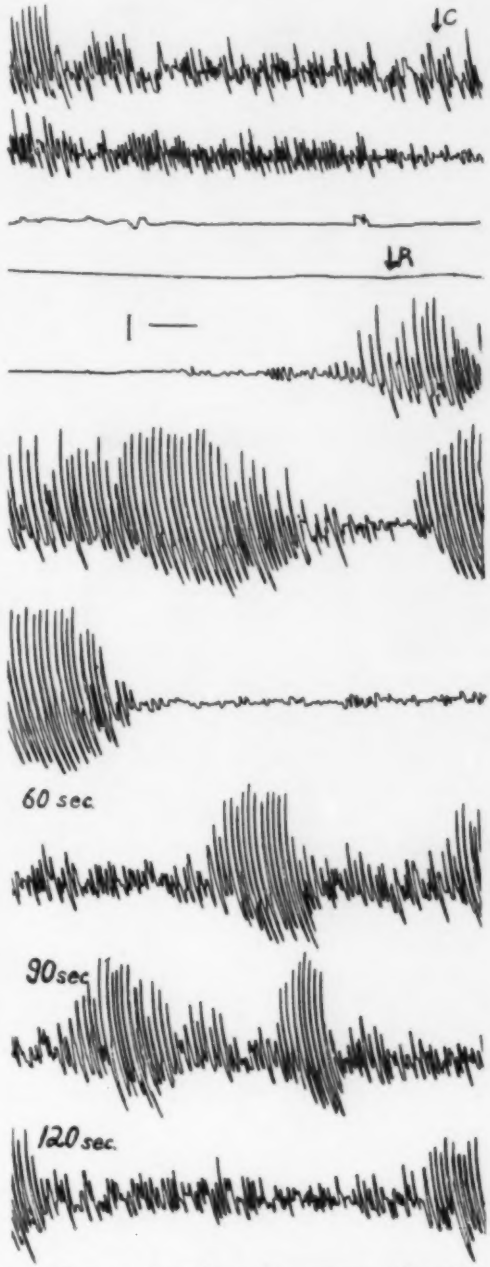

FIG. 1. Anoxia and recovery of motor cortex. First 7 strips continuous (70 secs.), lower 3 at indicated times after release. Carotid clamped at first arrow (C) released at second (R). In all figures, horizontal ruled line is 1 second and vertical is 100 microvolts. Read from left to right.

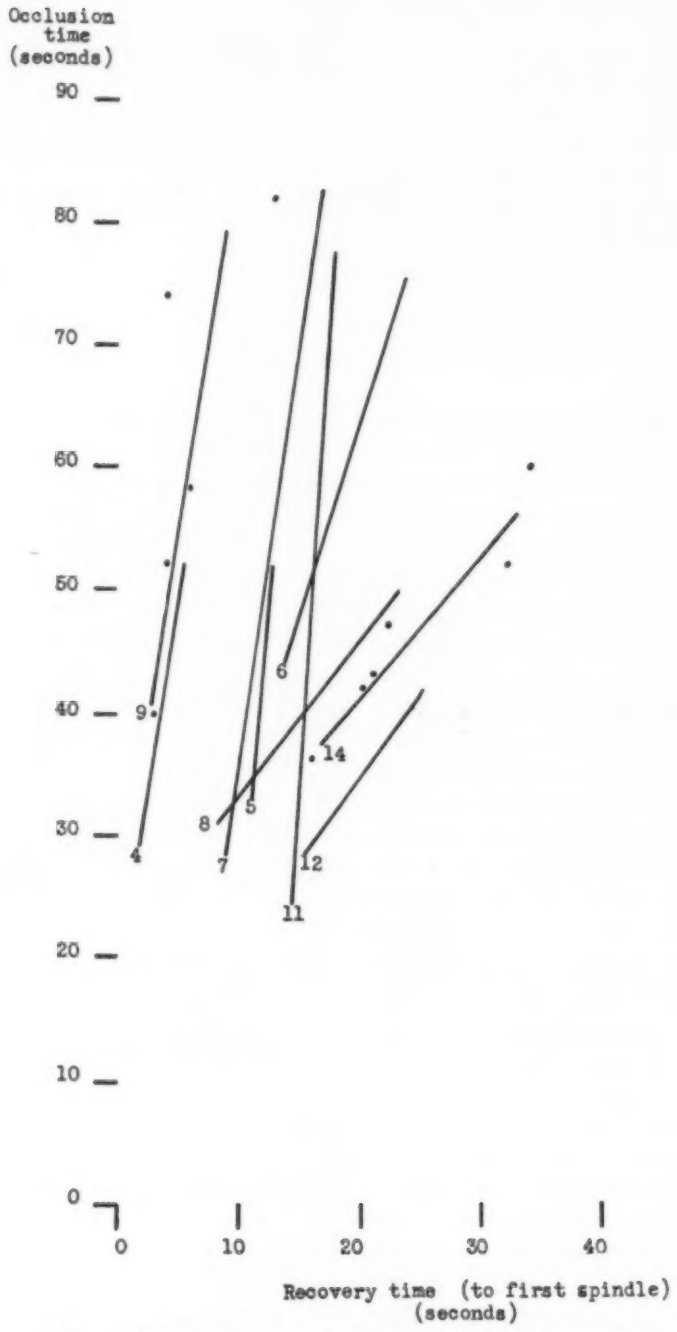

FIG. 2. Duration of recovery time as a function of duration of occlusion. The data indicate a linear relationship. The curves for individual animals seem to fall into two groups of different slope. Data for motor cortex, on nine cats (each one line). Observed points shown for cats 9 and 14; others (73 points) omitted. One aberrent animal not shown.

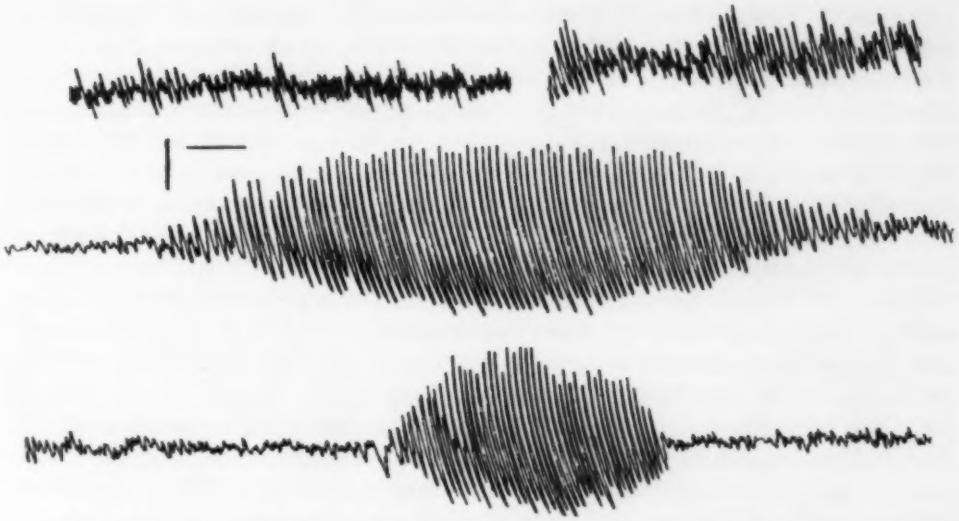

FIG. 3. Motor cortex. Upper left, before anoxia; upper right, 4½ minutes after release, amplitude still increased. Middle and bottom records, continuous strip from 10 to 40 seconds after release of a 30 second occlusion. Note gradual (first) and abrupt (second) start and end of spindles; also duration, regularity, amplitude and accelerating frequency in each.

and striking slow potential wave; appearing suddenly after the initially present waves have become flattened out, increasing to large amplitudes (60 microvolts from a previous level of about 20) during continued occlusion, and persisting for a minute or more into the post-anaemic period. These potentials start out coincident with the heart beat, but the individual wave, initially of rough sine form, is far longer and slower than any electrocardiogram element (Fig. 4), and as it grows in amplitude, a notch, or even two successively, ap-

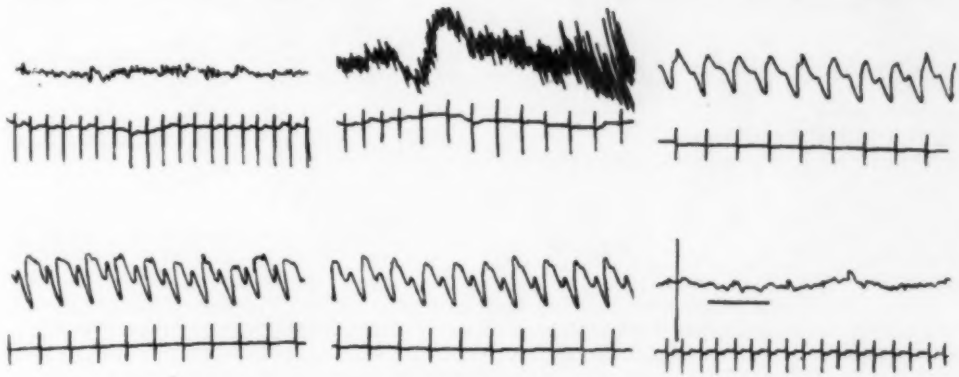

FIG. 4. Medulla, below obex (above) and electrocardiogram (below). Upper row, left to right: before occlusion, 5 secs., and 45 secs. after occlusion. Lower row: 70 secs. and 150 secs. after occlusion, and 45 secs. after release. Note high frequency waves early in occlusion followed by slow waves in time with heart beat.

pears on it. The absence of large arteries from this region, and the peculiar shape of the wave make it unlikely that this could be an arterial artifact (all the more so because the blood supply is clamped off); but it is much more probable that it is an artifact from the venous pulse, caused by movements of blood in the large posterior spinal vein nearby. Evoked potentials, from shining light in the eyes, as well as the spontaneous ones, were studied in the lateral geniculate body in relation to anaemia. The spontaneous waves, and the "on" and "off" discharges disappeared together after about 35 secs. of occlusion, and returned together following release.

Since our main interest in these experiments was to obtain survival times as an indication of the respiratory requirements of various brain masses, it was important to determine to what extent the anaemia acts via anoxia. Interruption of the blood supply causes a fall in available oxygen and glucose (of prime importance to brain) and a rise in CO_2 and other acids. Altered salt distribution is secondary to anoxia (Dennis and Mullin, 1938; Tupikova and Gerard, unpubl.) and changes in other substances are probably of lesser im-

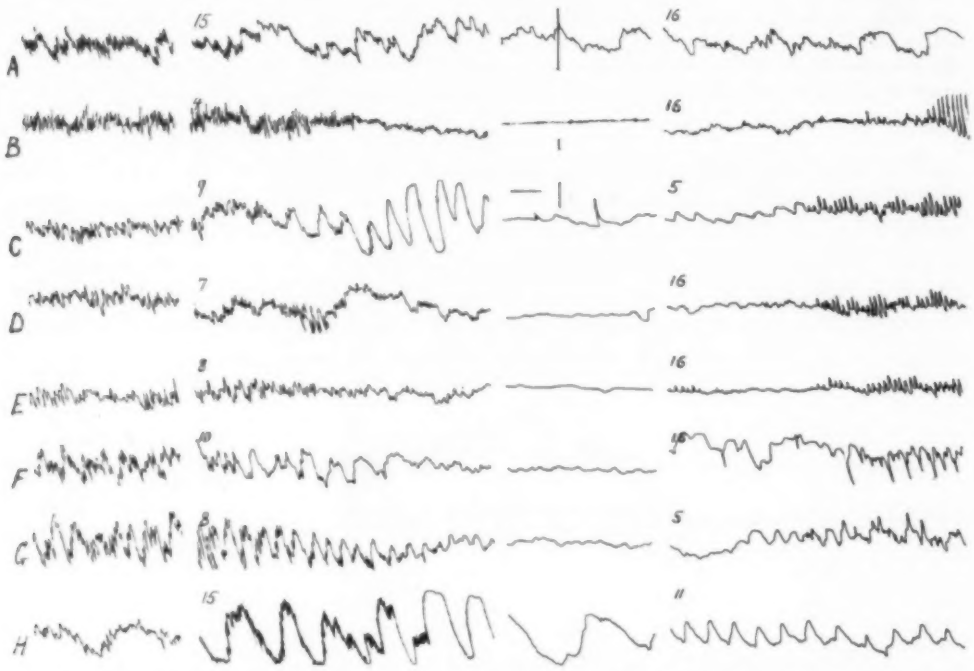

FIG. 5. Characteristic records from various brain regions. The first vertical column contains 5 sec. strips before occlusion; in the second column each strip is 10 secs. beginning at the indicated number of seconds after occlusion; the 5 sec. strips in the third column are from the 40th to the 45th sec. of a 50 to 70 sec. total occlusion period; the 10 sec. strips in the fourth column begin at the indicated number of seconds after release. The horizontal rows are from the following structures: A, cerebellar cortex; B, motor cortex; C, fascia dentata; D, lateral nucleus of the thalamus; E, dorsal nucleus of the thalamus; F, medial geniculate body; G, lateral geniculate body; H, spinal Vth tract in medulla. Note different amplifications for rows A and B; from C on all alike.

portance. Carbon dioxide accumulation has been shown to increase fast waves (Lennox, Gibbs, and Gibbs, 1938) and may contribute to the augmented high frequency potentials encountered early in anoxia. In sufficient excess, CO_2 also abolishes activity (Bremer and Thomas, 1936; Lennox, Gibbs, and Gibbs, 1936; Gerard, Marshall, and Saul, 1936). Hypoglycaemia acts much like (Gellhorn, Ingraham, and Moldavsky, 1938) and even directly induces (Himwich, *et al.*, 1938) a lowered oxygen usage, so it was especially important to evaluate this factor in anaemia.

If sugar depletion were the primary cause of the potential changes of anaemia, then increasing the blood sugar before occlusion should delay the potential changes. This was not the case: intravenous glucose up to two grams per kilo, administered just before occlusion, had no effect on the time relations or the changes seen. Lowered blood sugar (insulin, three units/kilo, one hour before occlusion), however, did alter the effects of anaemia. The early increase in rapid waves (and motor discharges) is advanced and augmented, total activity is lost sooner—*e.g.*, 23 instead of 33 sec. in the geniculate—and the post-occlusion spindles are delayed and less regular. Further, a large (30–50 μv), slow (0.7 sec.) wave with abrupt polarity changes appeared late in the anaemia period, after the base line had become flat, simultaneously in motor cortex and geniculate. It is likely that this wave is of the same nature as the slow waves occasionally seen after occlusion in other records, simultaneously in different parts of the brain which have not been showing synchrony, and represents blood movements.

Apart from occlusion, an interesting effect of anoxia was brought out by the insulin action, which initiated Cheyne-Stokes respiration. During the apnoeic intervals, cortical potentials showed spindles which faded to quiescence; with the resumption of respiration, the spindles returned, and activity was maximal as the respiration reached its peak. It seems probable, then, that anaemia acts mainly via anoxia if the blood sugar is not too low at the start;

Table I
Survival Times

Cephalic region	Time for disappearance of potentials (seconds)
Cerebellar grey	10–12
Ammon's horn	10–12
Cerebral grey (cortex)	14–15
Subcortical white matter	20–22
Corona radiata	20–25
Caudate nucleus	25–27
Ventrolateral nucleus of thalamus	28–33
Lateral geniculate body	32–37
Medulla: Reticular formation near n. vagus	30–40
tuberculum cuneatum	over 2 mins.
spinal V tract	over 2 mins.

Times given are for representative occlusions performed at the beginning of experimentation: successive occlusions lower these values from 1 to 5 secs.

and the different survival and revival times for particular regions are related to their oxygen needs. These times are shown in Tables I and II.

Table II
Recovery Times

Cephalic region	Time from release of occluded carotid to beginning of restoration of normal waves (seconds)
Corona radiata	4–6
Dorsal nucleus of thalamus	6–8
Rubrospinal tract	10
Optic tract	10
Lateral geniculate	12–14
Fascia dentata	12–15
Lateral nucleus of thalamus	15–17
Cerebral cortex	17–19
Cerebellar grey	23–25

Times given are for 55–79 second occlusions brought to one minute by comparison with simultaneously recorded motor cortex records. Because of the variations from cat to cat (see Fig. 2), the above, typical, values have been taken from one animal.

Though particular structures have their individual time and form characteristics for loss and return of potentials (Fig. 5), certain wave trains not uncommonly return simultaneously in several regions. In such cases, after anaemia, bursts appear together, repeated or with increasing asynchrony (Fig. 6). The motor cortex has at one time or another shown such synchrony with: the lateral nucleus of the thalamus, the lateral geniculate body, the corona radiata, the cerebellar grey, and the caudate nucleus (where, as in Fig. 7, the synchrony is much better after anoxia than before).

Discussion

That anoxia alone can abolish brain potentials is clear from experiments on breathing mixtures of low oxygen pressure by man (Davis, Davis, and Thompson, 1938; Gibbs and Davis, 1935; Hoagland, 1938), and cats (Derbyshire, Rempel, Forbes, and Lambert, 1936), as well as from the present evidence. The changes which follow sudden anaemia are primarily due to anoxia, but hypoglycaemia and especially hypercapnia may well contribute, as also may the increased extracellular potassium induced by anoxia (Tupikova and Gerard, unpubl.; Dubner, 1938; Libet and Gerard, 1938). We have not spefically eliminated possible effects of afferent impulses from the carotid body, following sudden occlusion of the common carotid, but there is no reason to suspect that these might evoke the changes seen, nor do so with specific time differences from one brain region to another.

The possibility must be considered that the differential survival times found are a result of incomplete anaemia, those regions receiving the most blood naturally surviving the best. The only source of a continued blood supply would be the anterior spinal artery, which was not specifically ligated.

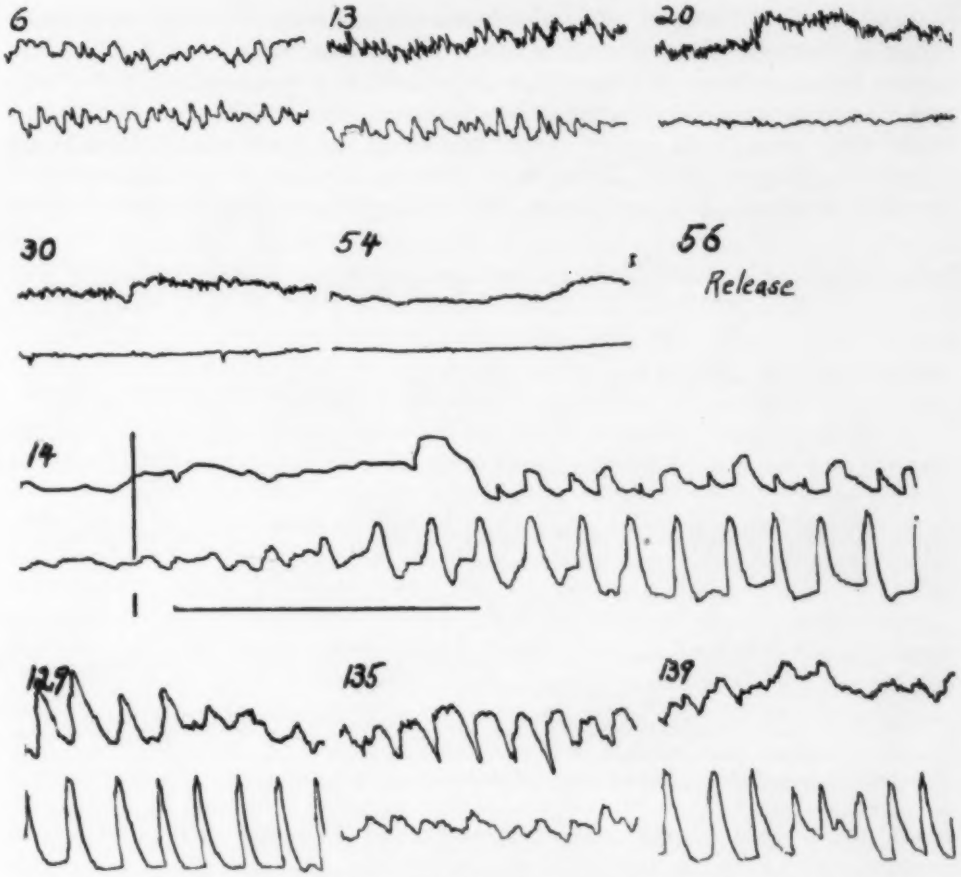

FIG. 6. Cerebellar (upper) and motor (lower) cortex records, faster speed. Note the greater amplification for the cerebellar records. Upper two rows, at indicated second after occlusion; lower two rows, same after release. Note high frequency waves in cerebellum are much increased during anoxia when motor cortex has already become quiescent. After anoxia, note marked synchronization of cerebrum and cerebellum but also, within a few seconds of one another, completely independent rhythms in either one of these structures.

This is normally very small in the cat and, in the neck region, derives its blood mainly from the vertebral arteries above the level of their ligation. The respiratory center lies in the base of the medulla in the direct path of any blood still passing in the spinal artery; yet in all cases in which the four large arteries are ligated (and not in those in which even a branch of an accessory vertebral escaped) respiration failed in 28–35 seconds after occlusion. Further, it has been shown (Stewart, Guthrie, Burns, and Pike, 1906) that in similar preparations, pigment injected intravenously into the peripheral circulation usually did not reach above C3 or C4 and never above the calamus. Yet under these conditions potentials from the cerebellum have persisted after medullary activity was abolished. It seems, therefore, that a continued circulation of small amounts of blood can have little if any influence on the present results.

The survival times of particular brain regions may than be taken as an index of their relative respiration rates. That these have been significantly altered by anaesthesia is improbable. Nembutal is a short-acting barbiturate and several hours elapsed between its administration and the start of observations; and, even at an earlier stage, this drug has little influence on brain potentials (Bremer, 1936; Derbyshire, Rempel, Forbes, and Lambert, 1936; Beecher, McDonough, and Forbes, 1938). Also, the unanaesthetised isolated

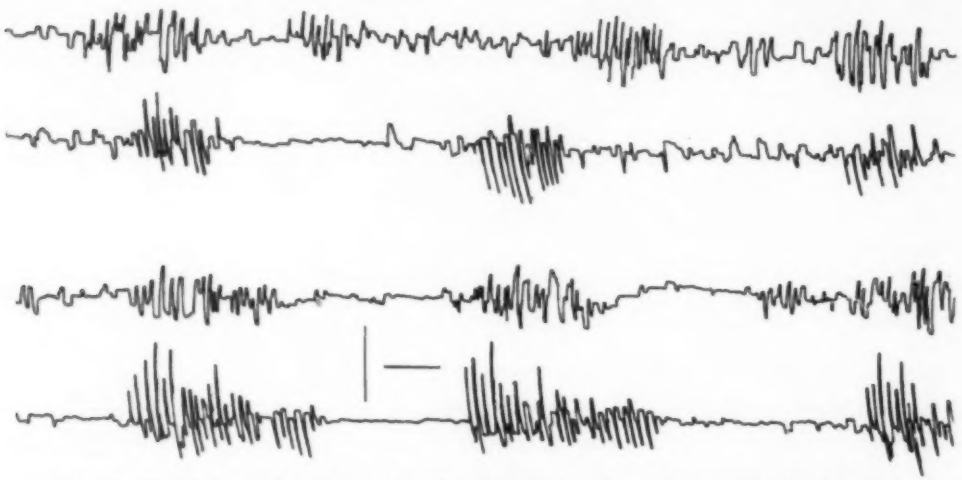

FIG. 7. Caudate nucleus (upper) and motor cortex (lower) records. Bipolar electrodes in each. Upper row before anoxia, lower row 45 secs. after release of a 52 sec. occlusion. Note imperfect synchrony before anoxia, more striking synchrony after.

brain preparation (Bremer, 1936; Bremer and Thomas, 1936; Bailey and Bremer, 1938) behaves much like the barbitalised one; and our present findings are comparable to those of Bremer except for the actual time scale. Since in the earlier experiments the blood supply was not completely eliminated (carotid occlusion only) or anoxia was produced by stopping artificial respiration, the longer intervals observed, as compared to the present ones obtained by sudden complete anoxia, are easily understood. Only a very partial or slowly developing anoxia could account for the long persistance of brain potentials and respiration found in the earliest work (Prawdicz-Neminski, 1925).

Survival times vary by a factor of four (over ten if all slow waves are included) from the shortest, in the cerebellar grey, to the longest, in the medulla. Arranged in order of decreasing times, structures fall into an anatomical sequence from "lower" to "higher" centers, or a phylogenetic one from older to newer (Pike, Guthrie, and Stewart, 1908a). The principal exception seems to be for the survival time of the cerebral cortex; which exception disappears in the revival time sequence (Heymans, *et al.*, 1937). The same general order, manifest when survival, revival or recovery times are considered, is met in mineral content (Alexander, 1938; Tupikova and Gerard, 1937) and in asphyxial degeneration determined microscopically; and, particularly, parallels

that for oxygen requirements, determined directly (Dixon and Meyer, 1936) or by histochemical reductions (Sugar and Gerard, 1938). There are, then, quantitative respiratory and other chemical gradients in the nervous system entirely comparable to the phylogenetic, anatomical, and functional ones that have long been recognized.

These findings also bear on the question of the differential susceptibility of synapses and so on their respiratory intensity. It is widely held that the synapse is uniquely sensitive to chemical insult and, partly on the basis of capillary richness of many neuropils studied, that it has an especially intense metabolism. This has been examined in detail elsewhere (Gerard, 1938) and the histochemical evidence has argued against this view (Sugar and Gerard, 1938). Here again it is seen that synaptic conduction persists well into the anoxic period, for optic impulses are recorded from the geniculate as long as the spontaneous rhythm is there and for some time after rhythmic potentials in the cortex have vanished. The afferent trains can be recorded from the thalamus while the thalamic cells are still able to respond, on advancing into or recovering from a period of anaemia. Even more striking are the findings (Bronk and Larrabee, 1937; Bargeton, 1938) that synaptic conduction through the cervical sympathetic ganglion can withstand over an hour of anoxia and fails no more rapidly than does conduction in non-synapsing fibers.

The increased electrical activity, especially high frequency waves, that appears during the earlier stages of anoxia, often parallels the motor signs of stimulation (hyperpnoea, clonus) but precedes them. The latter might represent either a release of the axial centers following depression of suprasegmental ones or a direct stimulation of the medullary and spinal ones, later in time because of their slower metabolism. An interval of 2 to 5 secs. between loss of cortical potentials and onset of clonus perhaps favors the second alternative. In the cortex itself, the augmented electrical activity is most probably a manifestation of the direct stimulating action of anoxia, comparable to the common early stimulation produced on a great variety of cells by depressant agents, and in this case implemented by a leakage of potassium ion from the cell interiors (Gerard, 1938b). A similar general enhancement of neuron excitation level, with more impulses summing at synapses or fewer required for effective passage, would help account for the widespread synchronization following anoxia. Separated brain regions lock into step presumably when a sufficient quantity of nerve impulses passes from one to the other or circulates between them; and increased neuron discharge or lowered synaptic threshold would favor this. What particular cells are responsible for the potential rhythms, even whether the same cells in different states of excitation or different cells active at different times (Blake and Gerard, 1937) produce the fast and the slow rhythms, the spindles and intervals, cannot be answered from these data.

Summary

Abrupt and functionally complete anaemia of the brain of cats was produced by temporary occlusion of one carotid after ligation of other vascular

channels; and the changes in potentials of known structures were observed during and after anaemia.

The survival time (duration of occlusion necessary to abolish electrical activity) varied four-fold from one brain region to another, though consistent for each, the "highest" and the newest ones failing first. There are gradients of metabolic intensity in the encephalon paralleling developmental, structural, and functional ones.

The recovery time (interval between restoration of circulation and return of potentials) for any structure increases with duration of the anaemia and with the number of preceding anaemia periods. Under equivalent conditions the recovery times for various brain regions fall into the same sequence as their survival times.

Anaemia acts primarily via anoxia, though hypoglycaemia and hypercapnia contribute. (Hypoglycaemia hastens the action of occlusion but hyperglycaemia is without influence.) The time values for change in function following altered oxygen supply indicate relative respiration rates of the structures studied. These relative rates are in agreement with those estimated in other ways.

During advancing anoxia brain potentials pass through a phase of increased frequency and often amplitude, indicating a transient stimulation en route to depression. Recurring large spindles follow anoxia, especially in the motor cortex. Another sign of increased excitation is an improved synchrony of potentials in widely separated structures.

Synapses are not especially sensitive to anoxia since, following occlusion, optic impulses persist at the geniculate, in secondary neurons, after unevoked potentials in the cortex have disappeared. The geniculate rhythm and responses to visual stimuli disappear and reappear together.

We wish to thank Mr. Elbert Tokaji for his assistance in these experiments and Dr. Franklin Offner for aid with the electrical apparatus.

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STUDIES ON CORTICOHYPOTHALAMIC RELATIONS IN THE CAT AND MAN

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INTRODUCTION

INTEREST in the hypothalamus has centered largely upon its function as an autonomic center mediating impulses which cause peripheral modifications of blood pressure, vasomotor states, visceral motility, etc., and upon the rôle of the cerebral cortex in inhibiting and augmenting hypothalamic functions. Experiments demonstrating release of cortical control of the hypothalamus, with resulting overactivity and "sham" emotional states, have been valuable in interpreting phenomena of emotional hyperactivity in man.[1] We have been interested in the reverse influence, namely the effect of hypothalamic activity upon the cerebral cortex in the intact animal, since an "emotional" influence on "thinking" is so commonly assumed in modern dynamic psychology.

ANIMAL EXPERIMENTS

The hypothalamus of an intact animal can be stimulated without traumatizing nervous tissue by means of the following technique.[2]*

STIMULATING TECHNIQUE

Cats were anesthetized with ether administered by tracheal cannula or, in most experiments, with nembutal, 65 mgm. per kg. body weight, intraperitoneally. The animals were fastened occiput down to an operating board by a special spring clamp which kept the snout down and the lower jaw maximally extended. The hypothalamus was approached by a trans-oral method. With experience, the soft tissue can be pierced by a probe in the proper location and spread apart. When the periosteum is stripped a small midline bleeding point may be seen in the posterior portion of the hard palate. This is an emissary vein lying in the rudiment of the old craniopharyngeal duct and hence just below the hypophysis and hypothalamus. A tapping instrument was used to make a few screw turns in the bone at this point and a small shell of hard bakelite threaded on the outside and with a ridge on its superior surface was screwed into place. The bakelite contained a nonpolarizing spiral of chlorided silver wire with a fresh wisp of cotton soaked with saline inserted in its core. The electrode did not pierce the bone. The silver wire, which extended through the superior surface of the bakelite as the primary lead, was entirely insulated by enamel.

In most of these experiments unipolar stimuli (induction shocks) were employed and the indifferent electrode was firmly attached to the shaven neck or screwed into the nasal bones. Carotid blood pressure and thoracic respiration were recorded as usual; and muscle movements, elevation of hair, dilatation of the pupils and movement of the nictitating membrane were observed. After the experiment the location of the electrodes was verified anatomically. In the majority of cases it was directly beneath the hypothalamus.

Forty-one cats were employed in these preliminary experiments. Rise in blood pressure was almost always obtained by passing induction shocks through the bone underlying the hypothalamus. Moderate stimuli (Harvard

* In these first experiments Dr. Sam Stein, Fellow in Neuropsychiatry, gave valuable assistance.

inductorium, 3 volts in primary, secondary at 7 to 9 cm.) produced a rise of 30 to 40 mm. Hg., in most cases unaccompanied by changes in respiration, diaphragm spasm or somatic muscular movements (Figs. 1 and 2). In an occasional animal isolated depression of blood pressure was observed. This atypical response could not be correlated with type of anesthesia, location of electrode or strength of current. No changes in blood pressure resulted from stimulation of the soft tissues or the periosteum of the hard palate, indicating that the blood pressure response was not a reflex to a painful stimulus. The heart rate was often accelerated or unchanged.

FIG. 1. Rise in blood pressure and increased respiratory rate resulting from induction shocks through the bone beneath the hypothalamus in the cat.

FIG. 2. Rise in blood pressure, increased cardiac rate and dyspnea during hypothalamic excitation from induction shocks passed through the underlying bone of the cat.

As previously found (Leiter and Grinker[3]), respiratory responses when present often consisted of a peculiar dyspnea. In some cases respiration was slowed or stopped. Usually the nictitating membrane retracted and the pupils dilated; only occasionally was a contraction of the pupils observed. These typical hypothalamic responses served to show that the hypothalamus can be stimulated through the bone in the intact animal, and under barbiturate anesthesia; and they suggested the possibility that hypothalamic potentials might be recorded under the same conditions.

RECORDING TECHNIQUE

After obtaining positive responses to stimulation, the hypothalamic lead was connected to an amplifier. A similar lead to a second channel was screwed into the occipital bone or over the frontal lobes to record cortical potentials. A common indifferent lead, identical in structure to the above, was screwed into the nasal bones. The electrical apparatus was made for us by Mr. Franklin Offner of the University of Chicago.[4] The two balanced, five-stage (all push-pull) resistance capacity coupled amplifiers drove two crystos graph ink-writing oscillographs (Offner and Gerard), of frequency range 0–150 vibration-per sec.; the time constant of the amplifiers was 0.5 sec. Low pass filter condensers were used in most experiments to remove frequencies greater than 25 per sec. In most experiments an amplification of 4 to 5 mm. per 100 microvolts (μv.) was used, although this varied somewhat.

Records from the cortical and hypothalamic regions (23 cats) are strikingly different so that either can be identified easily (Fig. 3).* The alpha rhythm of the cortex was often disturbed by sudden spikes of moderate voltage. The alpha waves appeared in bursts at the usual 10 to 12 per sec. frequency and

* In this and subsequent figures, simultaneous records from cortex and hypothalamus are illustrated with cortex in the upper tracing (C) and hypothalamus below (H). The time is constant: 17 mm. equal 1 sec. The perpendicular line represents the linear measurement of 100μv.

70 or more μv. in size; and sometimes interrupted by a few broad 3 per sec. waves of 50 to 60 μv. intensity. The hypothalamus, however, showed an irregularly but frequently appearing wave of 0.18 to 0.25 sec. duration, occurring 4 to 5 per sec. and 50 to 60 μv. in intensity. Superimposed on these were regular 13 per sec. waves of 12 to 15 μv. When the slow waves were of low voltage, bursts of alpha waves could be seen from the hypothalamic lead, but these were feebler than, and not synchronous with, those from the cortex and were fewer in number.

The hypothalamus could be stimulated by induction shocks, with the amplifier disconnected. Potential recording was possible within 7 to 8 sec. after the end of such stimulation. The hypothalamic slow waves increased 25 to 50 per cent in voltage and were accelerated from 4 up to 5 to 7 per sec.

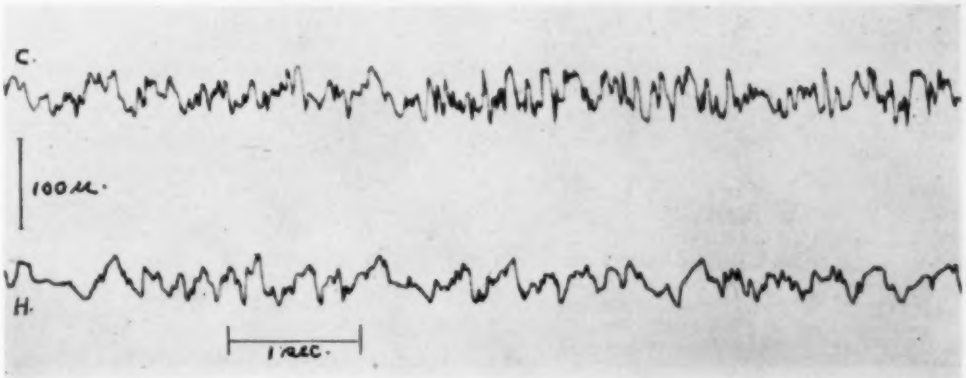

FIG. 3. Typical cortical and hypothalamic action potentials in the cat under nembutal anesthesia (C., cortex and H., hypothalamus), both obtained through the intact bone. In the cortical tracing bursts of alphas are visible as well as occasional broad waves. The hypothalamic curve shows broad 4 per sec. waves, superimposed on which are small 13 per sec. waves.

(Fig. 4). Giant regular cusp-like waves, of 150 to 200 μv. appeared sporadically but frequently, and other large 1 to 2 per sec. waves less commonly. Occasional bursts of alpha waves were observed, especially after stronger stimulation, which tended to synchronize with those of the cortex (Fig. 4, series 4).

Stimulation of the hypothalamus also affected the cerebral cortex by initiating fast beta waves which disappeared after several seconds. Large spikes and cusps at 4 to 5 per sec. were seen after moderate stimulation. The bursts of alpha waves became longer in duration and more sharply defined against the background; and each wave increased in voltage by 20 to 30 per cent, and became more regular and less broken by secondary waves. The cortical rhythm thus became plainer; for example, it was clear 40 to 50 per cent of the time before stimulation and 70 to 90 per cent after. Stronger currents tended to synchronize cortex and hypothalamus.

The hypothalamus was destroyed by piercing the bone under it and en-

circling it with a probe (Fig. 5). The result was a spectacular dropping out of almost all fast and slow waves. The alpha waves were reduced in voltage, but they became of greater duration, especially in the hypothalamic lead, and between their bursts only a few aberrant spikes appeared. Several minutes after the destruction, the alpha waves recovered in intensity and their bursts

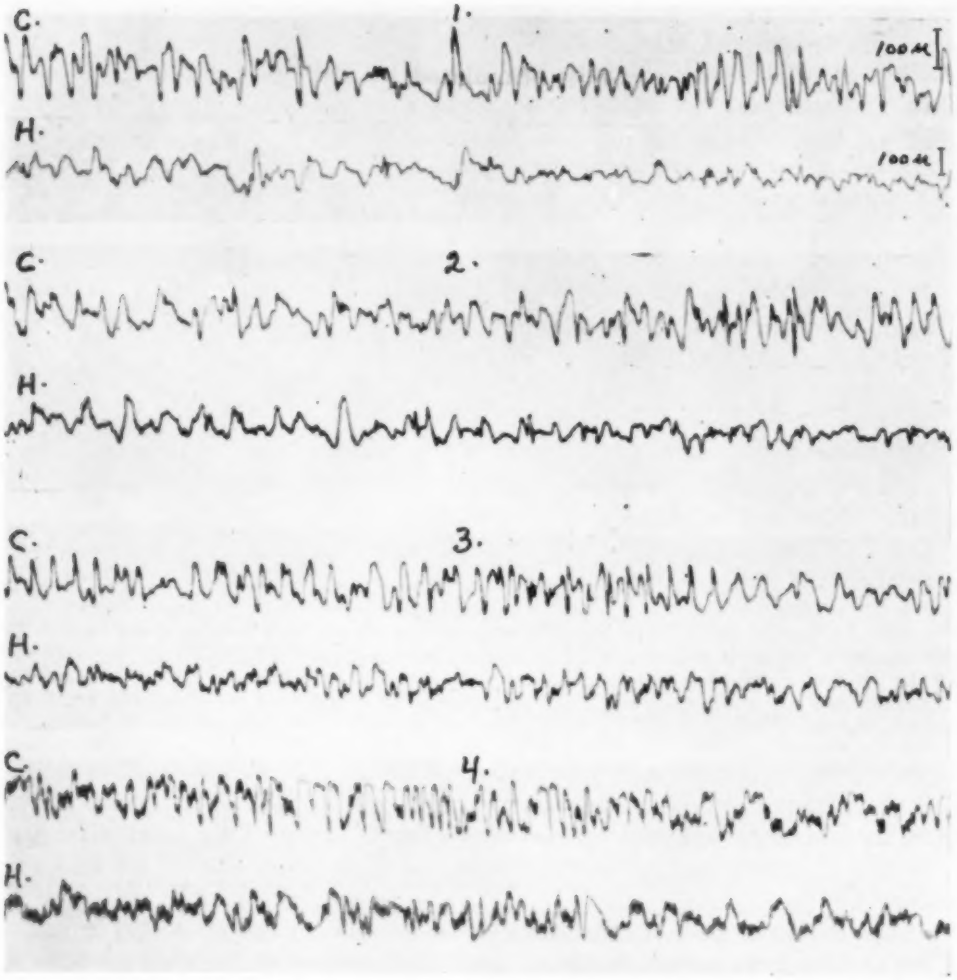

FIG. 4. The effect of stimulation of the hypothalamus of the cat through the bone: (1) before stimulation, (2) after stimulation with secondary coil of inductorium at 6.5 cm., (3) after stimulation with coil at 5 cm., (4) the same as (3) but with resulting partial synchrony of curves.

became sharply demarcated and synchronous in both leads. Stimulation of the base of the brain no longer affected cortical activity in the typical way, although in some instances it caused the alpha waves in both leads to become larger and more like spikes. The synchrony at both leads suggested that the cortical rhythms were spreading directly to the hypothalamic lead.

Pharmacological Experiments

The effects of adrenaline, eserine, ergotamine, pilocarpine, nembutal and metrazol on cortical and hypothalamic rhythms were next studied.

Adrenaline (Fig. 6). After injection of 0.4 cc. of 1/1000 per cent adrenaline intravenously the cortical rhythm changed from fairly regular alpha waves 8 to 10 per sec. and 60 to 70 μv. to less regular ones, 10 to 14 per sec. and 100 to 110 μv. Many fast waves also appeared and the alpha group showed rapid bursts with little interval between them. In 3 min. the fast waves disappeared

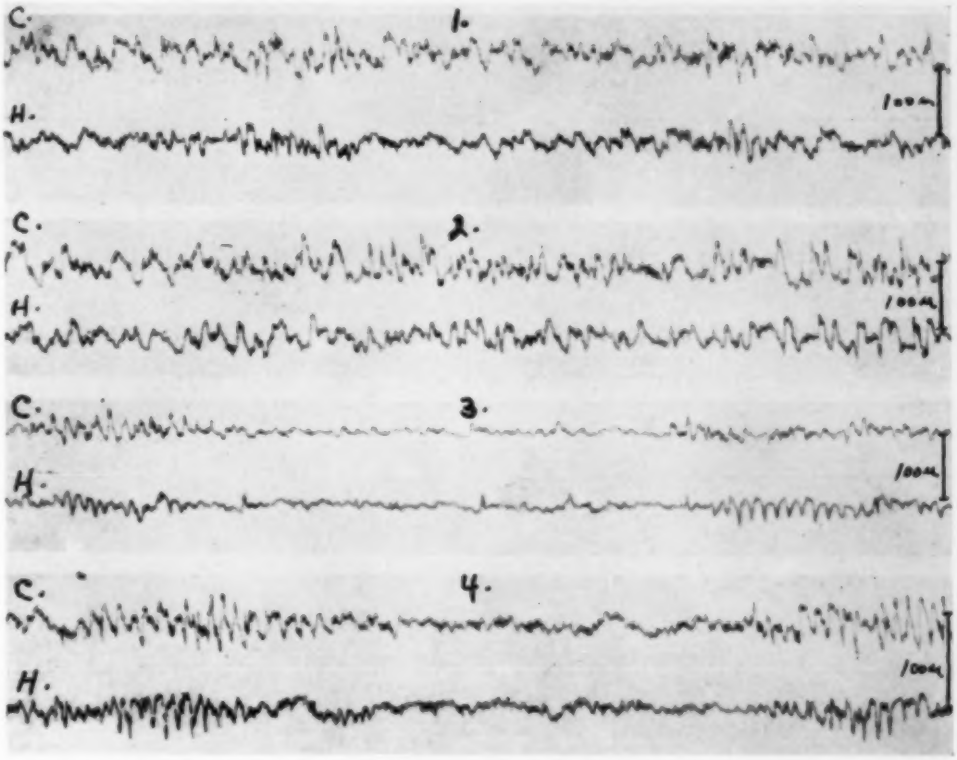

Fig. 5. The result of destruction of the cat's hypothalamus on currents obtained through the bone: (1) before destruction without stimulation, (2) stimulation with secondary coil at 8 cm., (3) thirty seconds after destruction of the hypothalamus, (4) stimulation of the hypothalamus as in (2) after destruction

and the original rhythm returned but with the alpha waves still large. The hypothalamic waves at 4 per sec. and about 30 μv., with occasional alpha sequences of 4 or 5 waves in 0.5 sec. at 40 μv., promptly gave way to waves of alpha frequency at 60 μv. somewhat synchronized with the cortical alpha waves along with faster waves. Three minutes later the alpha and fast waves had disappeared and the 4 per sec. rhythm reappeared and were larger than prior to injection. Adrenaline thus acted upon both the hypothalamus and cortex just as a powerful electrical stimulation of the hypothalamus. Perhaps the cortical effect is secondary, in both cases, to hypothalamic stimulation.

FIG. 6. The effect of 0.4 cc. of 1/1000 per cent adrenaline intravenously in the cat: (1) before injection, (2) immediately after injection, (3) three minutes after injection. Note the similarity of the effect to that of strong electrical stimulation of the hypothalamus as in Fig. 4, series 4.

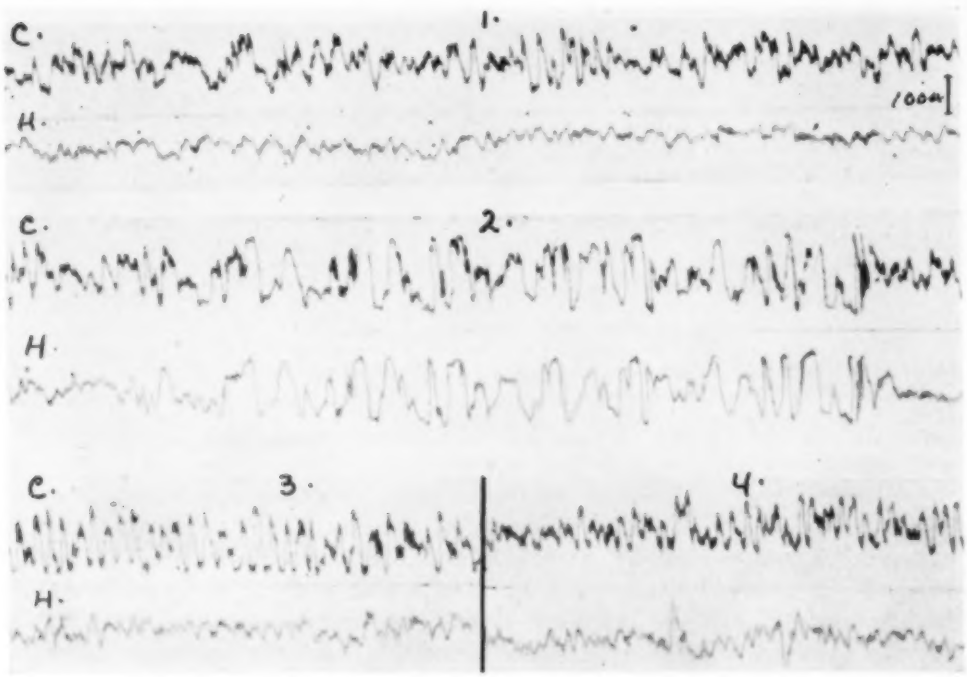

FIG. 7. The effect of 1.3 mgm. eserine injected intravenously in the cat: (1) before injection, (2) immediate excitement period, (3) 2.5 min. after injection, (4) 18 min. later.

Eserine (Fig. 7). Intravenous injection of 1.3 mg. of eserine caused slit-like pupils, marked ocular nystagmus and physical unrest. Hypothalamic and cortical potentials became synchronous and developed bursts of irregular coarse waves at 4 per sec. and more than 200 μv. in amplitude, with feebler waves at 15 or more per sec. superimposed. These bursts paralleled physical excitement and strongly suggested hypothalamic stimulation. Two minutes

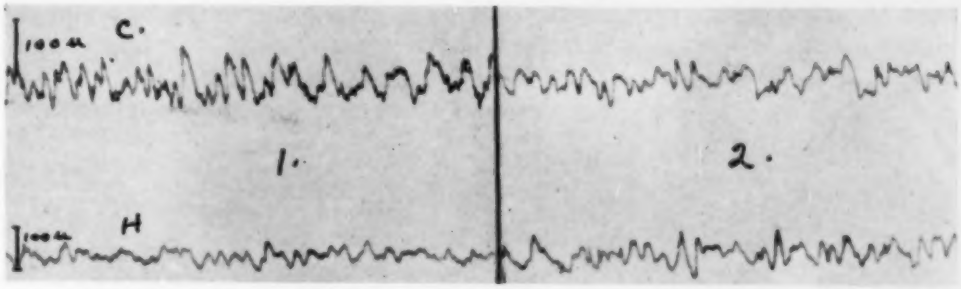

FIG. 8. The effect of 5 mgm. ergotamine injected intravenously in the cat, repeated in sixteen minutes: (1) before injection, (2) eight minutes after second injection.

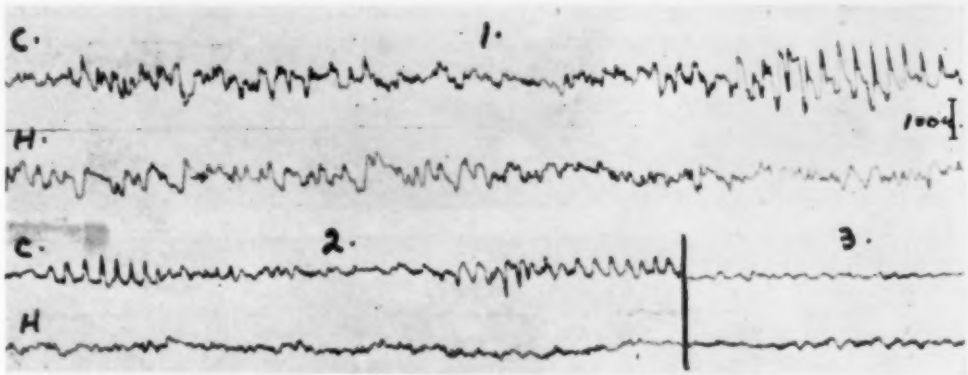

FIG. 9. The effect of 8 mg. pilocarpine injected intravenously in the cat: (1) before injection, (2) 16 sec. after injection, (3) 1 min. later.

later the hypothalamus quieted down to its normal pattern but with approximately double the pre-injection voltage; while the cortex continued to beat steadily and with great intensity for as long as twenty minutes before gradually declining. The cortical pattern consisted of giant alpha waves of 200 μv. intensity at 9 to 10 per sec., in regular steady rhythm without bursts (Fig. 7, series 3). After twenty minutes, the waves, still regular and continuous, had declined to 150 μv. Eserine thus produces a conjoint excitation of cortex and hypothalamus. The cortex first takes over the typical hypothalamic pattern, and in exaggerated intensity, and then returns to a normal cortical pattern, but still of greatly increased intensity. The hypothalamus shows a brief but intense increase in activity and quickly returns to its resting state.

Ergotamine (Fig. 8). Five mgm. of ergotamine were injected intravenously and the dose repeated in 16 min; only after another 8 min. were 10 per sec. alpha waves of 80 to 90 μv. in the cortex slowed to 6 to 7 per sec. and reduced to 50 μv. No fast waves appeared. The hypothalamic response, in contrast to that of the cortex, was excitatory and resembled greatly the effects of moderate stimulation.

Pilocarpine (Fig. 9). Eight mgm. of pilocarpine were injected intravenously; this was followed by sweating, salivation, constriction of the pupils (from 7 mm. to 3 mm. in diameter), and relaxation of the nictitating membrane. The effect on the cortex and hypothalamus was immediate. In 16.5

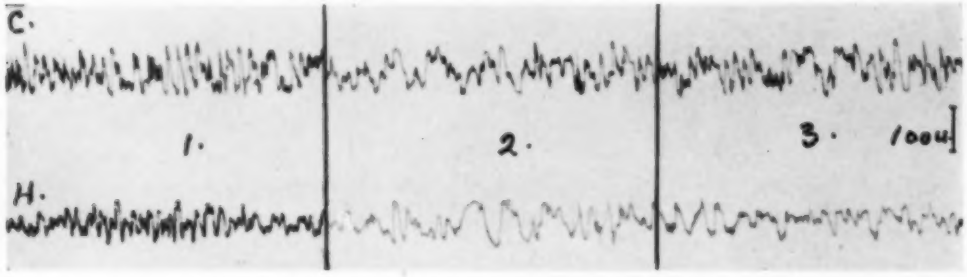

FIG. 10. The effect of 100 mg. nembutal injectedi ntravenously in the cat: (1) before injection, (2) after injection, (3) the effect of stimulation after nembutal injection.

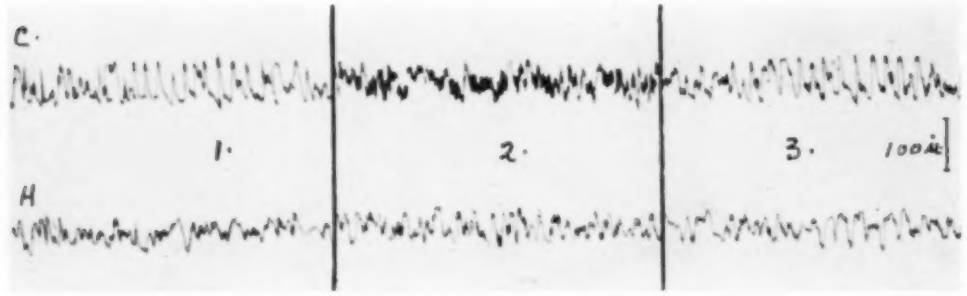

FIG. 11. The effect of 1 cc. of 10 per cent metrazol injected intravenously in the cat: (1) before injection, (2) 20 sec. after injection, (3) 60 sec. after injection.

sec. the hypothalamus showed barely measurable rapid waves at about 20 per sec., and after another minute the tracing was almost a straight line. The cortex showed the same initial pattern as the hypothalamus, but the pattern was interrupted by bursts of waves lasting about 1 sec. and recurring in 5.5 to 6 sec. These bursts were only half the size of the original alpha waves and more spike-like, but they retained their original frequency. After another minute these bursts had disappeared and the cortical tracing became also a straight line.

Nembutal (Fig. 10). One hundred mgm. of nembutal intravenously were superimposed on the original intraperitoneal injection. All fast waves were

promptly abolished, and the slow waves of both cortex and hypothalamus were slowed and enhanced. The effect was that of a slowing in time of 30 to 40 per cent with little change in intensity. The effect was still present 45 min. later, when hypothalamic stimulation seemed to counteract partly the nembutal effect.

Metrazol (Fig. 11). Intravenous injection of 1 cc. of 10 per cent metrazol solution resulted in very rapid respirations and convulsive movements of the forepaws and neck muscles. Both cortical and hypothalamic records showed signs of stimulation with abundant fast waves and increase in both preexisting frequencies (cortex, from 9 to 15 per sec.; hypothalamus, from 9 to 13). Cortical potentials decreased 20 per cent in amplitude and the hypothalamic ones increased by the same amount. After one minute the cortical potentials had returned to normal and those from the hypothalamus were of normal configuration though still of greater frequency and intensity.

Human Experiments

In the human the hypophysis and its overlying hypothalamus lie above or just behind the variable sphenoidal air sinus. This sinus ends posteriorly beneath the anterior clinoid processes or at most extends to a point below the middle of the floor of the sella turcica. It does not normally reach the posterior clinoids. The hypothalamus is thus closest to the base of the skull over the sella turcica and extending backward for a few millimeters. Between it and the dura, firmly attached to the bone, is a small subarachnoid space. Occasionally the anterior portion of the interpeduncular cistern extends this far anteriorly.

TECHNIQUE

The hypothalamic lead consisted of a sharply tipped steel drill rod 3 mm. in diameter and 16 cm. long with a slight upward concavity at its terminal third (Fig. 12). The rod was insulated to within 2 mm. of its tip with celluloid and Duco-cement and the exposed tip heavily silver-plated. A flexible enameled copper wire connected it with the amplifier. The cortical leads were silver spirals in the form of discs covered with electrode jelly, and fastened to the scalp with collodion. The resistance of such leads is less than 5,000 ohms. In some experiments silver wire earrings connected to a common wire were used as a reference lead for both occipital and hypothalamic leads. Insertion of the hypothalamic lead was easily accomplished. We are indebted to Dr. Samuel J. Pearlman for invaluable help in teaching us the technique. With the patient sitting the nasal mucous membranes were cocainized, the applicator being inserted to the posterior pharyngeal wall. At first an endoscope was placed in one nostril and the lead inserted with direct visualization by way of the other nasal passage. Later visualization became unnecessary and only one nostril was cocainized. The lead was passed carefully through the nasal passage and tipped upward when the posterior pharyngeal wall was reached (the exposed end of the electrode lay above and against the lower lip) to engage the pharyngeal mucosa at the junction of the roof of the pharyngeal vault and the posterior pharyngeal wall. With a forcible movement the needle tip was pushed through the mucous membrane, submucosa and periosteum into the sphenoid bone. A slight crunching sound and decreased mobility of the electrode indicate when it is firmly imbedded. The subjects feel a slight twinge of pain on insertion of the electrode but this soon passes off and they walk about comfortably for hours if necessary, with no interference with speech or swallowing.

The lead is removed with a sudden jerk and no subsequent antiseptic is necessary. The slight wound has never caused subsequent difficulty due to infection or hemorrhage. Two difficulties may be mentioned. If the electrode is not inserted high enough into the

vault a few strands of pharyngeal muscle are engaged and their action potentials obscure those from the hypothalamus. A large sphenoidal air sinus or an unusually shaped base of the skull mitigate against a successful registration of hypothalamic waves. The subjects lay relaxed and motionless on a couch in a darkened copper-screened room with eyes shut. For stimulation, the secondary coil (Harvard inductorium, 3 volts in primary) was pushed in during 10 sec. to 1 cm. (to avoid startle) and tetanization continued 5 to 20 sec. longer.

FIG. 12. The electrode used in stimulating the human hypothalamus through the underlying sphenoid bone.

Warning of a stimulation was given a few seconds in advance and only 2 or 3 stimuli applied to one person. Subjects for these experiments were obtained from general medical wards (excluding patients with debilitating or cardiac disease), or from the neuropsychiatric service.

Responses to stimulation

Stimulation of the hypothalamus produced a marked dilatation of the pupils, generalized hyperemia of the skin, copious perspiration, and a great rise in blood pressure. In one case the pressure rose 80 mm. Hg. during stimulation and took several minutes to return to normal. Evacuation of the urinary bladder occurred once, and in one subject body temperature rose to 103°F., and remained elevated for several days, without leucocytosis or other sign of infection. Strong stimuli evoked gradually increasing tonic spasms of the trunk and extremities, which did not outlast the current, sometimes accompanied by cyanosis. The spasms appeared only after stimulation had continued for several seconds and probably were due to spread to the cerebral peduncles or mesencephalon. Stimulation was painful due to current spread but subjects were willing to bear it for such brief periods. Controls showed that the responses described were not due to sensory stimulation.

Apart from transient pain responses, sometimes anxiety appeared during stimulation, and it persisted with crying and expressions of fear often for some minutes. In one subject protracted sobbing occurred. Several patients saw their lives pass before their eyes, as has been described in drowning. In general, the affective state accompanying hypothalamic stimulation could not be correlated with the rage attacks in human encephalitics, the manic responses from operative manipulation of the hypothalamus or the sham rage of cats.

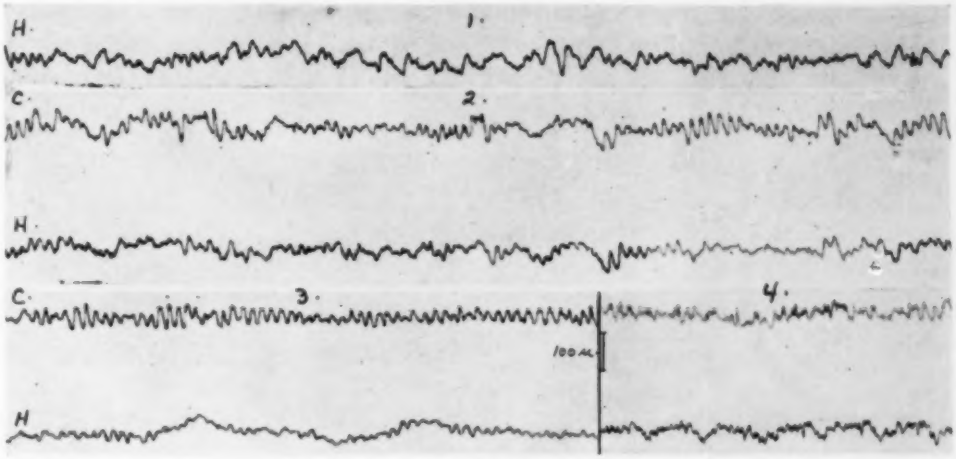

FIG. 13. Four types of human hypothalamic patterns compared with simultaneous cortical tracings. In (1) there is no accompanying cortical curve, the broad 4 per sec. waves are characteristic; (2) alpha hypothalamic rhythm is shown in contrast to that of the cortex; (4) shows undulations in the hypothalamic tracing.

Cortical potentials were more or less dominated by the 10 per sec. rhythm which was also frequently clear in the hypothalamic record (Fig. 13). Hypothalamic alpha waves tended to accompany cortical waves, but they were not as frequent and never of as high a voltage (Fig. 13, series 2). Besides the

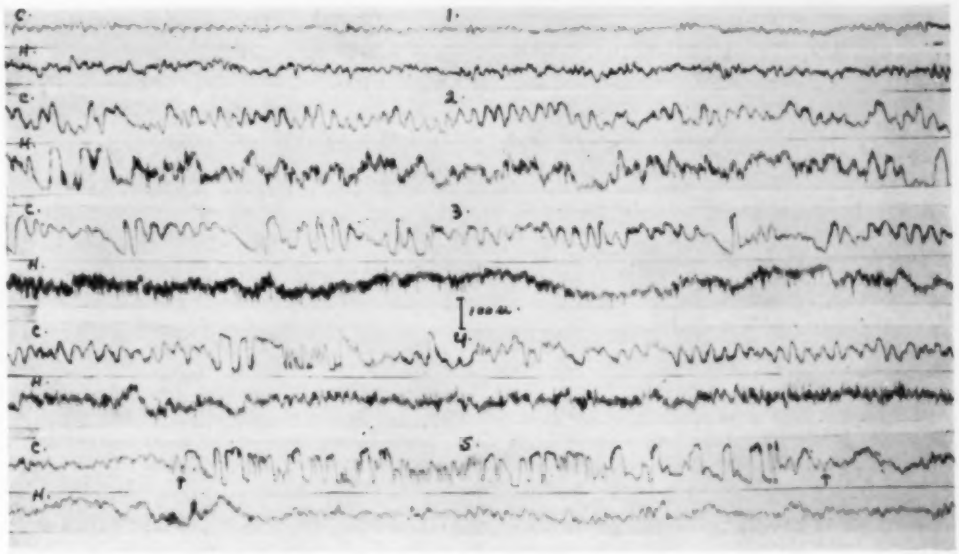

FIG. 14. Cortical and hypothalamic electrograms in the human: (1) before stimulation, (2) immediately after stimulation, (3) 4 min. later, (4) 7 min. after stimulation, (5) 9 min. after stimulation showing a recurrent wave of excitation after the curve had returned to its pre-stimulation level (within arrows).

alphas there were slower coarser 4 to 6 per sec. waves of 30 to 50 μv. intensity in the hypothalamus (Fig. 13, series 1); and occasional larger waves and coarse undulations occurred once every 0.6 to 0.8 sec. (Fig. 13, series 4). In general

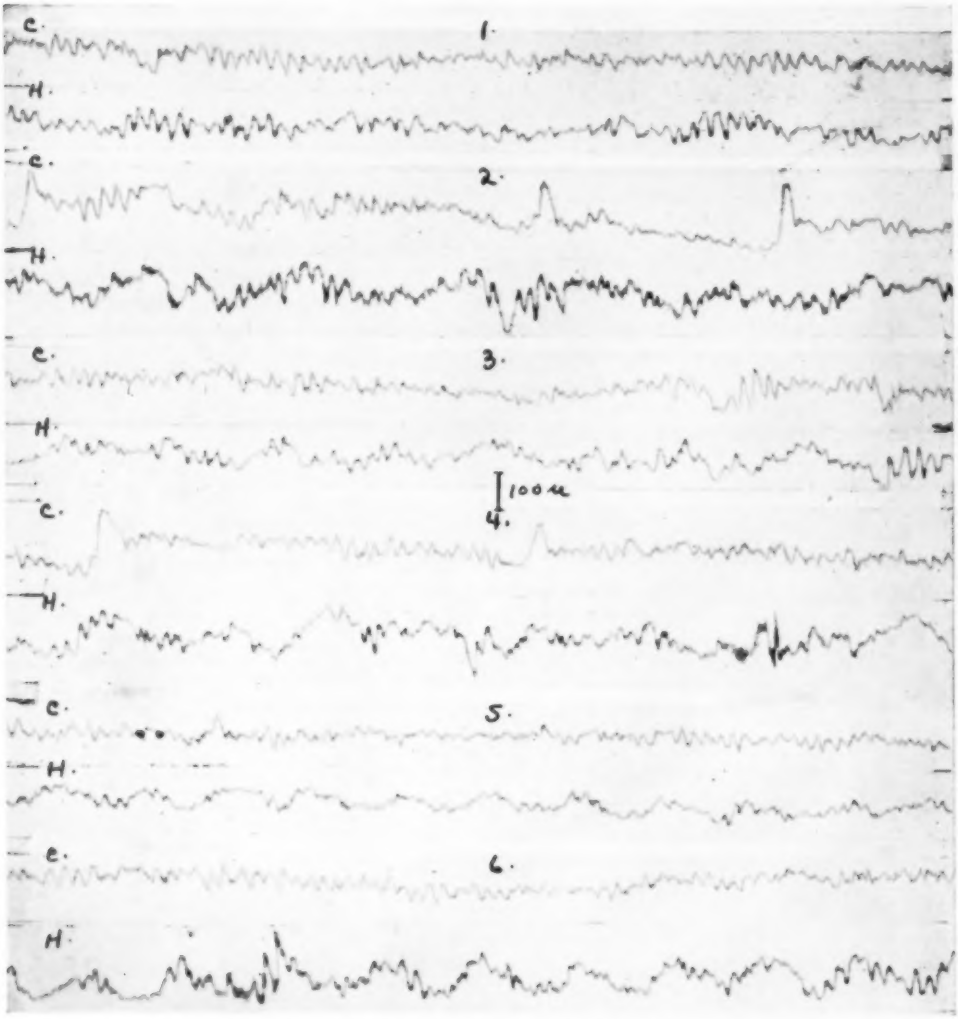

FIG. 15. Cortical and hypothalamic electrograms in the human: (1) before stimulation, (2) immediate effect of stimulation, (3) 2 min. later, (4) 4 min. after stimulation, (5) 5 min. after stimulation, (6) second stimulation with little effect on cortex.

the human "resting" hypothalamus beat like that of the cat with 4 per sec. waves as the "typical" characteristic, but for each subject the hypothalamic record was more individual than that of the cortex and probably more characteristic than a given cortical pattern.[5] In several cases only alpha waves appeared before stimulation, but following it they were replaced by the

typical hypothalamic curve. Hypothalamic alpha waves, in contrast to those of the cortex, are slightly intensified and more continuous with the eyes open than with them shut (Fig. 18).

Electrograms

Hypothalamus. Stimulation was followed by increased excitation in the hypothalamic electrogram (Figs. 13–16). A marked increase of fast waves uncountable at the ordinary recording speed almost always thickened the record for several minutes and disappeared gradually (Figs. 14[2,3,4] and 15[2]). Immediately after stimulation the waves became extremely irregular and any alpha rhythm which had been present completely disappeared. The 4 per sec. waves also became irregular and usually doubled their amplitude. In some persons an undulation appeared at 70 per min. at 30 μv. intensity. This was

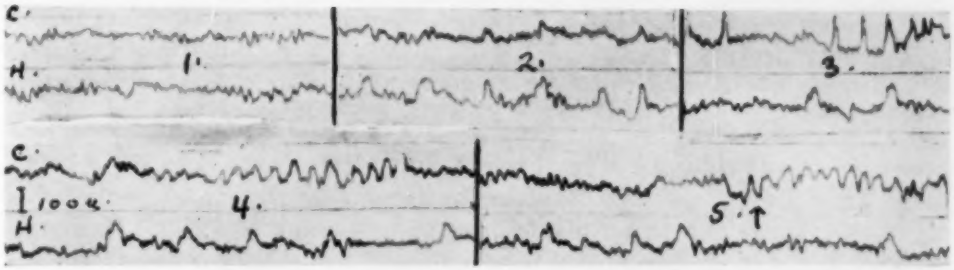

FIG. 16. Cortical and hypothalamic electrograms in the human: (1) before stimulation, (2) immediately after stimulation, (3) 4 min. after stimulation, (4) 5 min. after stimulation, (5) 7 min. after stimulation, showing a burst of cortical excitation in the midst of a quescent period.

considerably slower than and not to be mistaken for the pulse rate (Fig. 15[5,6]). Sometimes the hypothalamic rhythm was interrupted by giant waves (200 μv.) and the entire curve for several minutes was synchronous with that of the cerebral cortex (Fig. 17[2]); as in the cat after strong hypothalamic stimulation.

The late effects of hypothalamic stimulation were equally interesting. The 70-per-min. wave sometimes lasted several minutes, disappearing and returning again. More frequently the large giant waves disappeared and a modified alpha rhythm of low voltage reappeared, but interrupted irregularly by large rounded slow waves at 2 per sec. (Fig. 16). This pattern might continue for several seconds, or fade and return. An occasional train of fast waves was often seen, and occasionally large spikes or cusps appeared for 1 to 2 sec. and were followed by quiescent periods of a minute or more. The general impression was that, after the initial excitation had subsided, increased hypothalamic activity reappeared in short, recurrent, irregular periods.

Cortex. As a result of hypothalamic stimulation the cortical alpha rhythm was sometimes interrupted by large rounded 100 to 120 μv. waves, lasting 0.3 sec. and appearing once in 2 or 3 sec. (Figs. 15 and 16). These continued

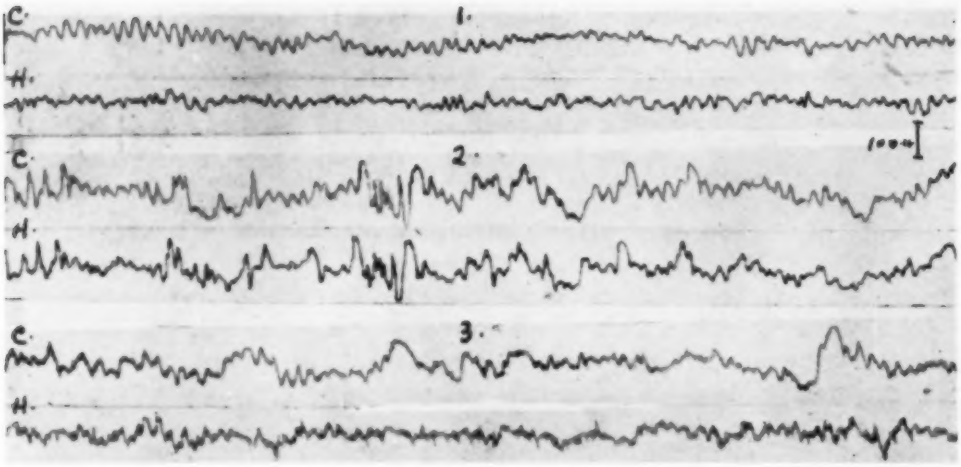

FIG. 17. Cortical and hypothalamic electrograms in the human: (1) before stimulation, (2) synchronized immediate effect of strong stimulation, (3) 6 min. after stimulation reappearance of excitation after curve had become quiescent as in (1).

to appear sporadically for several minutes, becoming more and more infrequent. Large irregular undulations also appeared after stimulation and gradually straightened out to normal during several minutes (Fig. 17). Large rounded waves, with the alphas superimposed, sometimes occurred 6 to 8 min. after stimulation. In a few cases, spikes of 100 μv. and 4 per sec. appeared in the cortex in phase with the rounded large waves in the hypothalamus, even 4 or 5 min. after stimulation. The alpha waves themselves were gradually slowed, to 5 per sec. and intensified, as much as four fold. Giant waves of 200 to 250 μv. appeared as individuals, later in groups lasting for several seconds interspersed between large alpha waves, and still later in ten second trains erupting in the midst of a normal rhythm (Figs. 14 and 16).

An attempt was made to excite the hypothalamus by strong emotions (Fig. 19). A subject was told that a sex habit, regarding which he had considerable anxiety, had probably irreparably damaged him. Both cortical and hypothalamic curves became irregular and partially synchronous, and giant

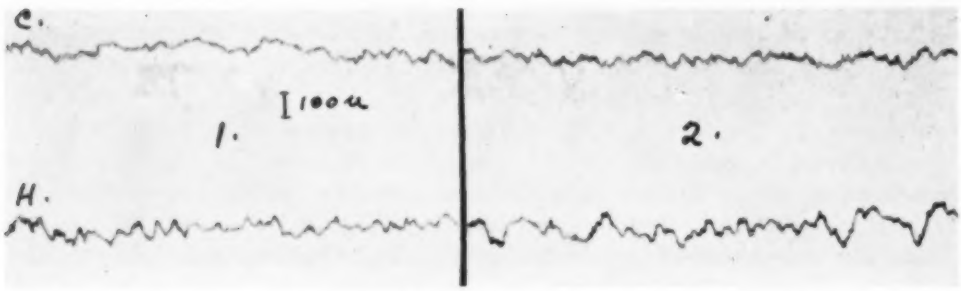

FIG. 18. In (1) subject has his eyes shut; in (2) he has opened his eyes.

waves and plateaus with frequent cusps appeared. After several minutes the hypothalamus was still beating irregularly with numerous spikes and cusps (Fig. 19, series 3 at arrow). An electrical stimulation of the hypothalamus in-

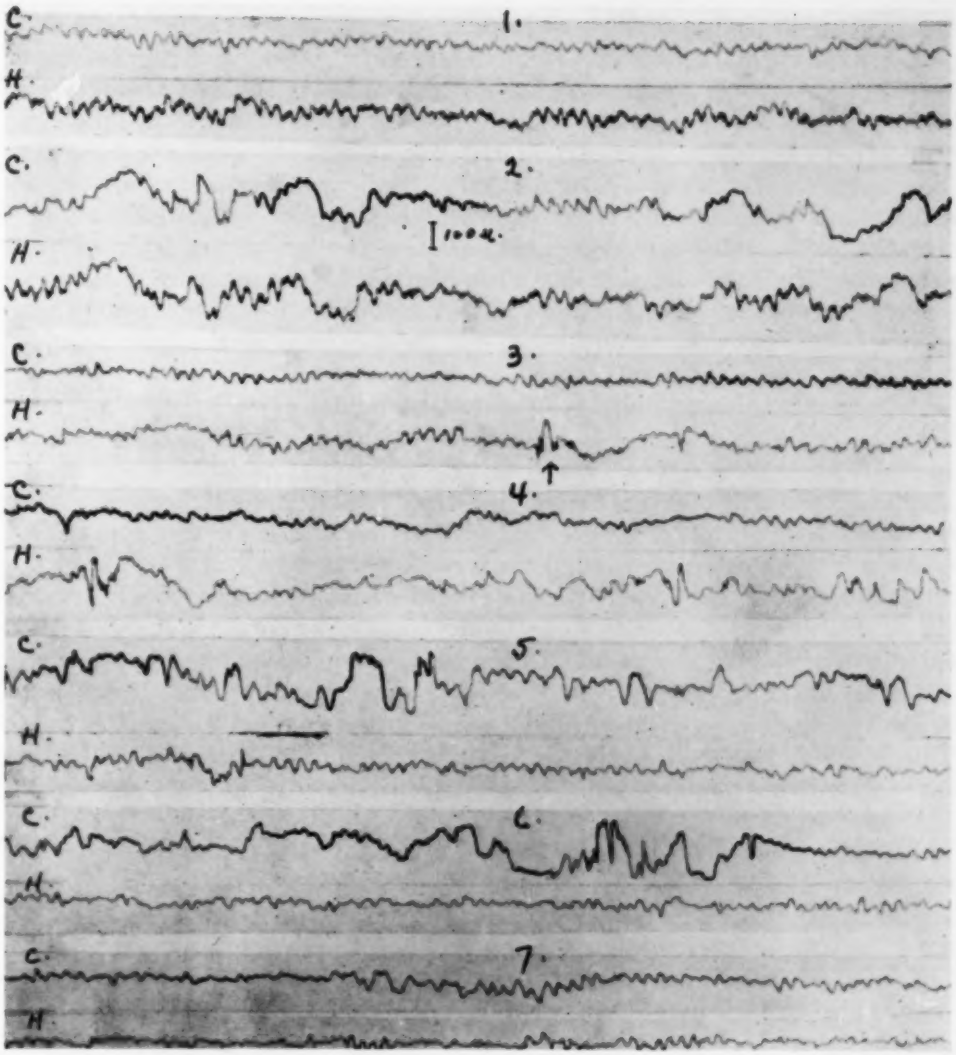

FIG. 19. Same patient as in Fig. 15: (1) resting curve, (2) after crucial emotional stimulus administered verbally, (3) reassurance, arrow indicates aberrant cusp and spike, (4) electrical stimulation, (5) 6 min. after electrical stimulus, (6) 7 min. after stimulation, (7) return quiescent stage ten minutes after stimulation.

duced immediate changes in this region and delayed ones in the cortex, appearing 6 min. after stimulation and subsiding in another four, which paralleled those resulting from the emotional stimulus (Fig. 19).

Discussion

This method for stimulating the hypothalamus through the base of the cranium is useful in animals since it is simple, easily performed, requires no operation, and can be used acutely on a conscious animal. It is adapted rather for study of the hypothalamus as a whole and does not permit the localization possible with the Horsley-Clarke instrument. In the intact human, however, this is the only method available for stimulating the hypothalamus or leading off its action potentials. It should prove possible to follow the influence of ideational stimuli with emotional coloring, as here reported, and to study the effects of direct electrical stimulation of the hypothalamus on the peripheral autonomic system by observing heart-beat, gastro-intestinal motility, secretion and vascular changes, bladder and ureteral tone, temperature, sleep, etc. The hypothalamic lead may also aid in the study of excitatory processes in epilepsy and irritative lesions, assist in more accurate localization of intracranial neoplasms and further our knowledge of corticohypothalamic relations in mental disturbances.

The spontaneous potentials of the cat and human hypothalamus are predominantly slow waves at 4 to 5 per sec. and at 0.9 per sec. Small waves at 13 to 15 per sec. and the alpha rhythm are variable. The alpha waves probably originate in the hypothalamus, for they are of different frequency and regularity than the cortical ones, though after destruction of the hypothalamus cortical alpha waves seem to reach the basal electrode.

Stimulation of the hypothalamus evokes a massive discharge which persists or reappears for minutes after the stimulation is over. This suggests that this structure serves as a reservoir for prolonged excitation and has a chronic influence on brain and periphery. Affect-laden ideational stimuli similarly cause hypothalamic excitation which precedes and outlasts the cortical ones. The results indicate a "driving" of cortex by hypothalamus parallel to the well recognized overwhelming of intellectual processes by emotional activity.

The changes in cortical potentials produced by hypothalamic excitation, increased voltage of the alpha waves and appearance of large, slow waves are suggestive of the "disintegrated curves" described for schizophrenia and organic brain disease.[6] The alpha pattern of the normal human cortex is not fixed and can be profoundly modified by hypothalamic stimulation even to the point of resembling pathological curves. The more detailed psychiatric parallels to and interpretations of these findings will be reported elsewhere.

Summary

1. A method has been described for stimulating the hypothalamus and recording its electrical activity in the intact cat and man.

2. The hypothalamic electrogram is specific and differs from the cortical electrogram.

3. Epinephrine, eserine, ergotamine, pilocarpine, nembutal and metrazol produce characteristic changes in these electrograms.

4. Electrical stimulation of the hypothalamus increases the hypothalamic potentials at once and in recurrent long-lasting bursts. A similar effect on the cortex is probably secondary to the hypothalamic one.

5. Ideational emotion-laden stimuli produce effects on hypothalamus and cortex similar to those elicited by electrical stimulation of the hypothalamus.

6. Strong electrical or emotional stimuli result in extensive synchronous discharge of hypothalamus and cortex.

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EFFECTS ON ELECTROENCEPHALOGRAM OF VARIOUS AGENTS USED IN TREATING SCHIZOPHRENIA*

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THE GROSS LACK of information concerning the mechanism of action of various agents now used in treating schizophrenia has been a stumbling block in otherwise rapid progress toward understanding this disorder. The present study was undertaken with the object of seeing what changes, if any, were caused in brain wave patterns of schizophrenic patients subjected to insulin hypoglycemia, metrazol, intravenous sodium amytal, carbon dioxide inhalation and emotional stimulation. Although electroencephalograms obtained from schizophrenic patients fall within normal limits, there is a definite tendency towards a weak alpha (10 per sec.) rhythm in this disorder.[1,2,3,4,5] Hoagland, Rubin and Cameron[6] and Yeager and Baldes[2] have also shown that 1 to 5 per sec. delta waves are usually increased during the more severe phases of the schizophrenic illness. The significance of these characteristics of the electroencephalogram in schizophrenia will be discussed later.

RESULTS

Insulin hypoglycemia. Electroencephalograms (EEG) were obtained during insulin hypoglycemia in 15 schizophrenic patients. Twelve of these cases showed a definite weakness of the alpha rhythm before treatment (Fig. 1A). In the initial excitatory stages of the hypoglycemic reaction, the alpha rhythm was strengthened (Fig. 1B), and then as the reaction deepened into coma, the alpha waves were replaced by 1 to 5 per sec. delta waves characteristic of depressed cortical activity (Fig. 1C). Termination of the hypoglycemia by glucose was followed within 1 to 3 hours by a "rebound" strengthening of the alpha rhythm of variable duration in 10 of the 12 cases showing a weak alpha rhythm before treatment (Fig. 1D). Gerard[7] and Bremer and Thomas[8] have demonstrated a similar post depression enhancement of the cortical rhythms in animals.

Although clinical improvement was maintained in 9 of the cases responding to treatment, the alpha rhythm always reverted to its pretreatment level within from 1 to 4 weeks after discontinuing the treatment (Fig. 1E). The 1-to-5 per sec. delta waves were present in 6 of these 15 cases before treatment. They were eliminated by the treatment with no recurrence, except in one case that relapsed and again showed delta wave activity. This is in agreement with the findings of Hoagland, Rubin and Cameron.[6]

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Metrazol. It is difficult to study the effect of metrazol on the EEG because it is virtually impossible to record during the convulsion. Small subconvulsive doses of metrazol, however, increase alpha wave activity (Fig. 2B) and the postconvulsive depression is followed by a temporarily enhanced alpha rhythm similar to that following insulin coma (Fig. 2C). Here again the alpha

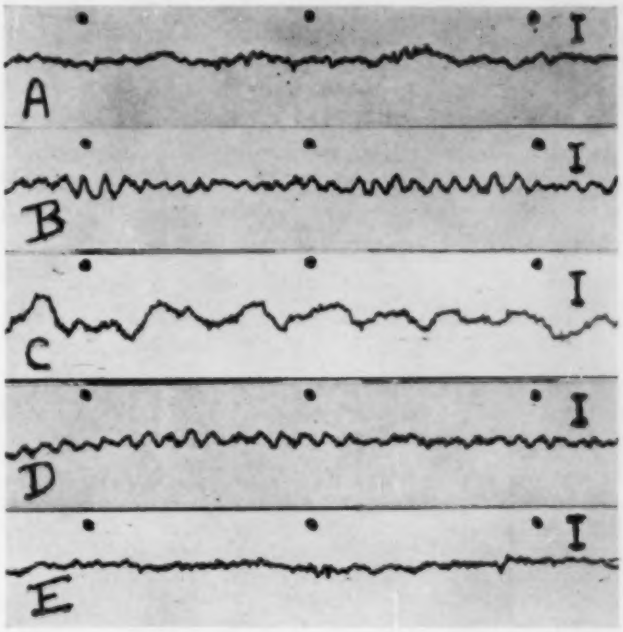

FIG. 1. Record from a schizophrenic patient undergoing insulin shock treatment. A. Before insulin. B. Strengthening of alpha rhythm during initial excitatory stages of hypoglycemic reaction. C. Large 1 to 5 per sec. delta waves associated with hypoglycemic coma. D. Two hours after termination of the hypoglycemic reaction. "Rebound" activation of alpha rhythm. E. Three weeks after discontinuing insulin hypoglycemia treatment. The record has reverted to its pretreatment appearance, although the patient has maintained his clinical remission. The slow 1 to 5 per sec. delta waves are less in evidence than in A. The dot time markers are in seconds and the vertical measure at the side represents 50μv. potential. This and subsequent records are read from left to right.

wave activity eventually reverts to its pretreatment level after treatment (Fig. 2D). Similar changes in the EEG following the injection of metrazol (or its physiological equivalent, camphor) have been described by Fischer and Löwenbach[9] in animals and Gibbs, Gibbs and Lennox[10] in man.

Intravenous sodium amytal. Sodium amytal given slowly intravenously in schizophrenic patients (Fig. 3) accentuates the alpha rhythm during the prenarcotic stage of its action. This runs parallel to the clinical improvement

with increased accessibility and rapport. As medication is continued, and the patient becomes drowsy, the alpha waves break up into faster, more irregular waves, interspersed with delta waves.

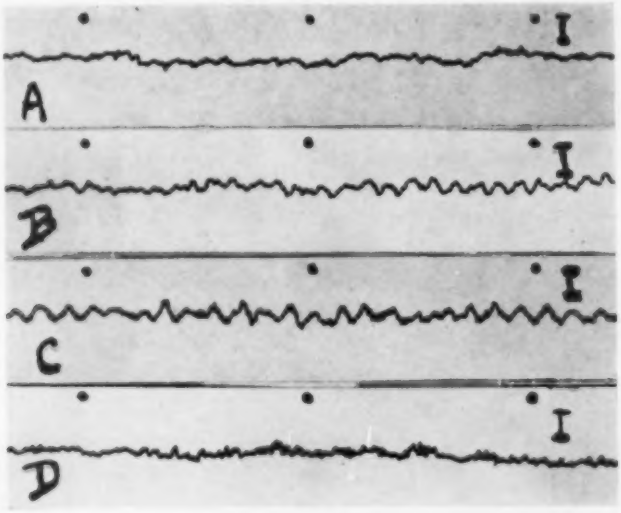

FIG. 2. Record from a schizophrenic patient. A. Before metrazol. B. During administration of subconvulsive dose of metrazol. C. 2 hours after metrazol convulsion, and D 5 days after last metrazol convulsion. The alpha rhythm is temporarily strengthened by the metrazol.

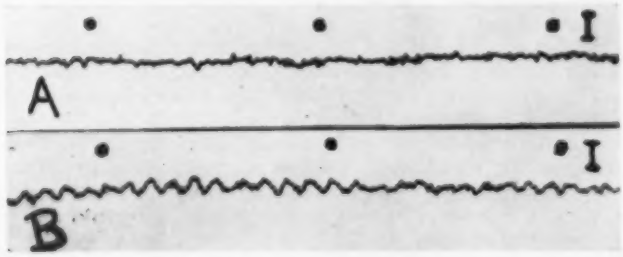

FIG. 3. Record from a schizophrenic patient. A before and B after subnarcotic dose of sodium amytal given intravenously.

Carbon dioxide inhalation. The inhalation of carbon dioxide also produces an accentuation of the alpha rhythm during the preliminary excitatory stages of its actions on schizophrenic patients (Fig. 4B). If unconsciousness is produced, the alpha rhythm again breaks up into fast waves superimposed on slower delta waves (Fig. 4C).

Emotional stimulation. There are many different types of emotional stimulation. Strong anxiety or agitation seems to preclude the development of an alpha rhythm.[1] On the other hand, milder, anticipatory, interest-producing,

and enthusiasm-arousing emotions, such as those caused by visits from relatives, the anticipation of going home, or the excitement of the first few weeks in a new environment, seem to strengthen the alpha rhythm (Fig. 5). Inter-

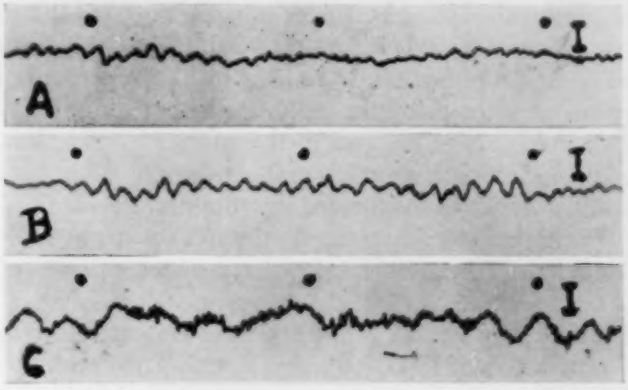

FIG. 4. Record from a schizophrenia patient. A before, B during the initial excitatory phase and C during coma produced by the inhalation of carbon dioxide.

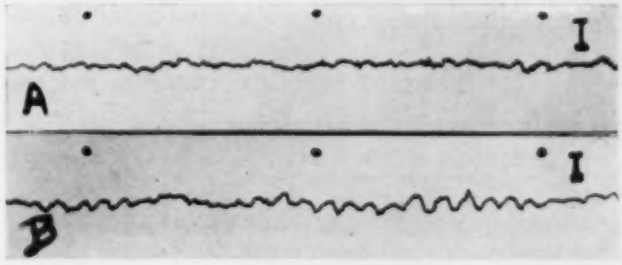

FIG. 5. Record from a schizophrenic patient. A before and B after being told that he was going to be discharged from the hospital. Shows effect of mild emotional stimulation on the alpha rhythm.

estingly enough it is just this type of interest-arousing affective situation that seems temporarily to help schizophrenic patients the most.

DISCUSSION

It is apparent that the agents commonly used to influence the schizophrenic process favorably seem temporarily to strengthen the weak alpha rhythm found in this disorder. One can only speculate concerning the significance of this finding. The work of Adrian[11] strongly suggests that alpha waves are produced by neurons of the resting visual cortex beating in unison over an area of at least one centimeter in diameter. A weak alpha rhythm, therefore, would indicate poor neuron synchronization[12,13] and, inasmuch as brain wave patterns seem to be inborn,[5,14,15] one might reasonably conclude

that poor cortical neuron synchronization is an inherent neurophysiological characteristic of schizophrenic patients.[16]

Gerard[12] and Jasper[17] have shown that cortical rhythms are strongest at certain optimum levels of excitation above which, or below which, the rhythms drop out. That the weak alpha rhythm of schizophrenia is due to a low rather than a high level of excitation is indicated by the fact that the agents investigated all exert their beneficial clinical effect on the schizophrenic symptoms during the preliminary (or postcomatose) excitatory stage of their action on the cortex and the alpha rhythm. It is probable that insulin, metrazol, sodium amytal and carbon dioxide depress cell oxidation with resulting anoxia and an increase in excitation followed by depression of the cortical neurons.[12,18,19,20,21,22] The action of emotional stimulation is less easily understood, but it possibly results from activation of the cerebral cortex by the diencephalon.[16]

The failure of the various treatment procedures to maintain a strengthened alpha rhythm would appear especially significant. This strongly suggests that the treatments used thus far are only temporary in their action, and that they fail to produce a lasting alteration in the fundamental neurophysiological defect of the weak alpha rhythm found in schizophrenia. As soon as the treatment is finished, the alpha waves return to their original pretreatment level, although a clinical remission may appear to have occurred.

Summary and Conclusions

1. Although brain waves from schizophrenic patients fall within normal limits, there is a definite tendency toward a weak alpha rhythm in this disorder.

2. This weakness of the alpha rhythm in schizophrenia would appear to be an inborn neurophysiological characteristic of schizophrenia. The alpha rhythm is temporarily strengthened by insulin hypoglycemia, metrazol, intravenous sodium amytal, carbon dioxide inhalation and emotional stimulation—agents which sometimes seem favorably to influence the schizophrenic process.

3. The failure of these agents permanently to strengthen the alpha rhythm in schizophrenia suggests, however, that they produce only temporary benefit. This may be sufficient to cause a remission, but the fundamental neurophysiological defect evidently persists in a latent form even after "successful" clinical treatment.

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